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Signed Andrew Gerry

Dated 2 September 2003

Patents Form 1/77

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11DEC02 E769948-1 D01298
P01/7700 0.00-0228787.8

Request for grant f a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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1. Your reference

   PC25420

2. Patent application number
   (The Patent Office will fill in this part)

   0228787.8

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

   PFIZER LIMITED
   Ramsgate Road,
   Sandwich,
   Kent, CT13 9NJ

   Patents ADP number *(if you know it)*

   United Kingdom 6892673001

   If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

   MORPHOLINE DOPAMINE AGONISTS

5. Name of your agent *(if you have one)*

   Dr. J.E. Rutt

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

   UK Patent Department
   Ramsgate Road,
   Sandwich, Kent,
   CT13 9NJ
   United Kingdom 7908676002

   Patents ADP number *(if you know it)*

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is not named as an applicant, or
   c) any named applicant is a corporate body.
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Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	75
Claim *(s)*	0
Abstract	0
Drawing *(s)*	0

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature J.E.Rutt Date 19 November 2002

12. Name and daytime telephone number of person to contact in the United Kingdom — Dr. J.E. Rutt 01304.48020

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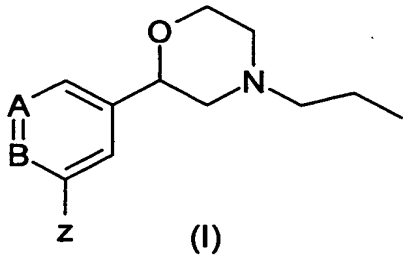
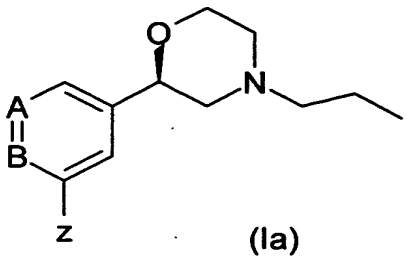
Morpholine Dopamine Agonists

The present invention relates to a class of dopamine agonists, more particularly a class of agonists that are selective for D3 over D2. These compounds are useful for the treatment and/or prevention of sexual dysfunction, for example female sexual dysfunction (FSD), in particular female sexual arousal disorder (FSAD) and male sexual dysfunction, in particular male erectile dysfunction (MED). Male sexual dysfunction as referred to herein is meant to include ejaculatory disorders such as premature ejaculation, anorgasmia (unable to achieve orgasm) or desire disorders such as hypoactive sexual desire disorder (lack of interest in sex). These compounds are also useful in treating neuropsychiatric disorders and neurodegenerative disorders.

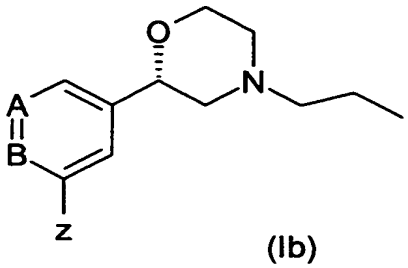
The present invention provides for compounds of formula (I), (Ia) and (Ib)



(I)



(Ia)



(Ib)

Wherein:

A is selected from C-X and N,

B is selected from C-X and N,

X is selected from HO, $C(O)NH_2$, NH_2
Y is selected from H, HO and F
Z is selected from H, HO, F, $CONH_2$ and CN;
And pharmaceutically acceptable salts, solvates and prodrugs thereof;
With the provisos that:
for a compound of formula (I), (Ia) or (Ib), when A is C-X and B is C-Y, at least one of X, Y and Z must be OH;
for a compound of formula (I), when A is C-X and B is C-Y, Y is H and Z is H, then X cannot be OH.

The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and the base salts thereof.

A pharmaceutically acceptable salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of the formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, p-toluenesulphonate and pamoate salts.

Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.

For a review on suitable salts see Berge et al, J. Pharm. Sci., 66, 1-19, 1977.

The pharmaceutically acceptable solvates of the compounds of the formula (I) include the hydrates thereof.

Also included within the present scope of the compounds of the formula (I) are polymorphs thereof.

A compound of the formula (I) contains one or more asymmetric carbon atoms and therefore exists in two or more stereoisomeric forms.
Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

Preferred compounds of the present invention are compounds of formula (Ia) and (Ib)

Particularly preferred are compounds of formula (Ia)

Preferably A is C-X and B is C-Y or N
More preferably A is C-X and B is C-Y

Preferably X is OH

Preferably Y is H

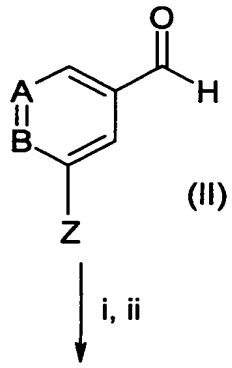
Preferably Z is selected from H, HO and F.
More preferably Z is selected from H or OH.

Particularly preferred are compounds (and salts thereof) of the present invention:

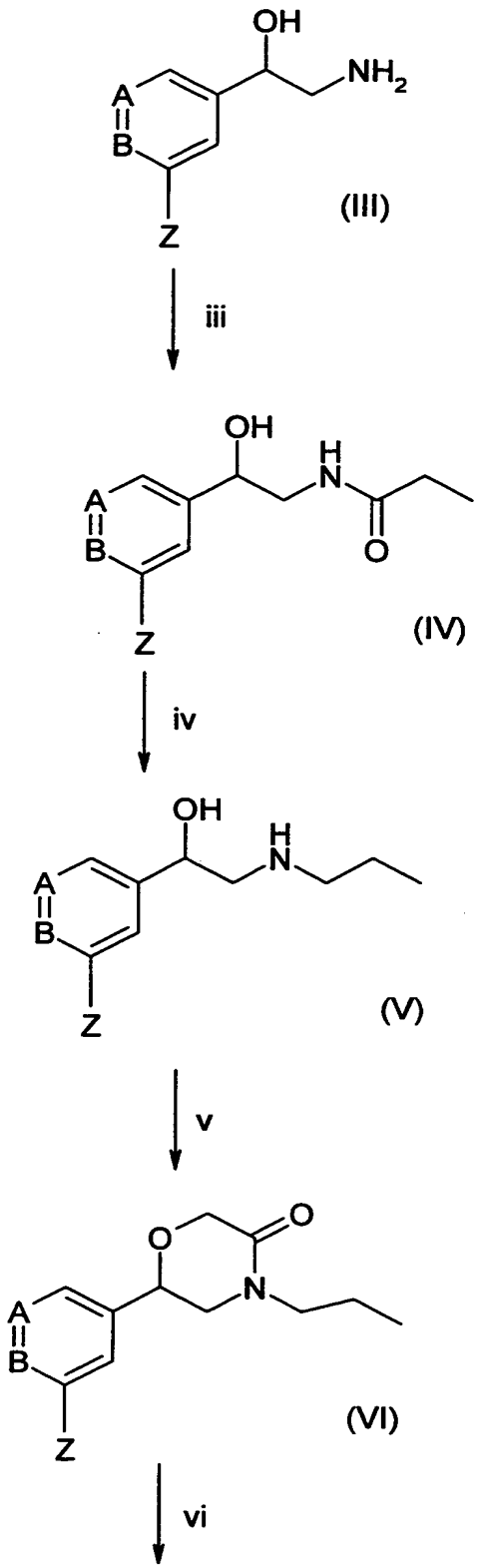
R-(-)-3-(4-Propylmorpholin-2-yl)phenol (Example 7a)
S-(+)-3-(4-Propylmorpholin-2-yl)phenol (Example 7b)
R-5-(4-Propylmorpholin-2-yl)benzene-1, 3-diol (Example 15a)
S-5-(4-Propylmorpholin-2-yl)benzene-1, 3-diol (Example 15b)
R-(+)-2-Fluoro-5-(4-propylmorpholin-2-yl)phenol (Example 23a)
S-(-)-2-Fluoro-5-(4-propylmorpholin-2-yl)phenol (Example 23b)
2-Bromo-4-(4-propylmorpholin-2-yl)phenol (Example 30)
2-Hydroxy-5-(4-propylmorpholin-2-yl)benzamide (Example 35)
2-Nitro-4-(4-propylmorpholin-2-yl)phenol (Example 36)
2-Amino-4-(4-propylmorpholin-2-yl)phenol (Example 37)
5-(4-propylmorpholin-2-yl)pyridin-2-ylamine (Example 44)

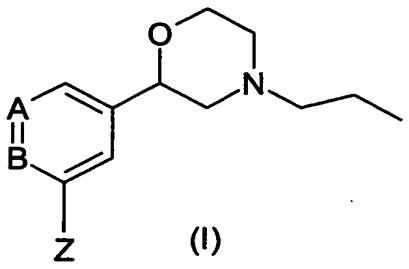
Compounds of the invention may be prepared, in known manner, in a variety of ways. The routes below illustrate methods of synthesising compounds of formula (I); the skilled man will appreciate that compounds of formula (Ia) and (Ib) may be isolated with appropriate resolution techniques.

Compounds of general formula I where A is C-X, B is C-Y, where X, Y and Z are as described herein may be prepared according to reaction scheme 1.



(II)


OH
NH2
A
B
Z
(III)
iii
OH
H
N
O
(IV)
iv
(V)
v
O
(VI)
vi



(I)

Scheme 1

Compounds of formula (III) may be prepared by reacting an aldehyde of formula I with i) a cyanide source or nitromethane followed by ii) reduction with borane, lithium aluminium hydride or hydrogenation. Some compounds of formula II are also commercially available.

Compounds of formula (IV) may be prepared by reacting compounds of formula (III) with iii), acid chlorides in the presence of a suitable base such as triethylamine or 4-methylmorpholine. Typical reaction conditions comprise 1.0 equivalents of amine (III), 1.2-2.0 equivalents of base (preferably triethylamine), 1.1-1.3 equivalents of acid chloride in dichloromethane at 25°C.

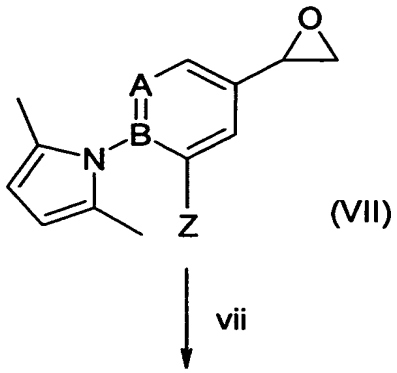
Compounds of formula (V) may be prepared by reducing compounds of formula (IV) with iv), reducing agents such as borane or lithium aluminium hydride. Typical conditions comprise 1.0 equivalents of amide (IV), 1.2-3.0 equivalents of borane in THF at reflux. Compounds of formula (V) can also be made by reductive animation of compounds of formula (III) with a suitable aldehyde in the presence of sodium cyanoborohydride.

Compounds of formula (VI) may be prepared by reacting compounds of formula V with v), chloroacetyl chloride in the presence of base such as triethylamine, sodium carbonate and potassium hydroxide. Typical conditions comprise 1.0 equivalents of amine IV, 1.2-2.0 equivalents of triethylamine in dichloromethane at 25°C, the crude reaction mixture is then dissolved in IPA with 1.2-3.0 equivalents of aqueous potassium hydroxide.

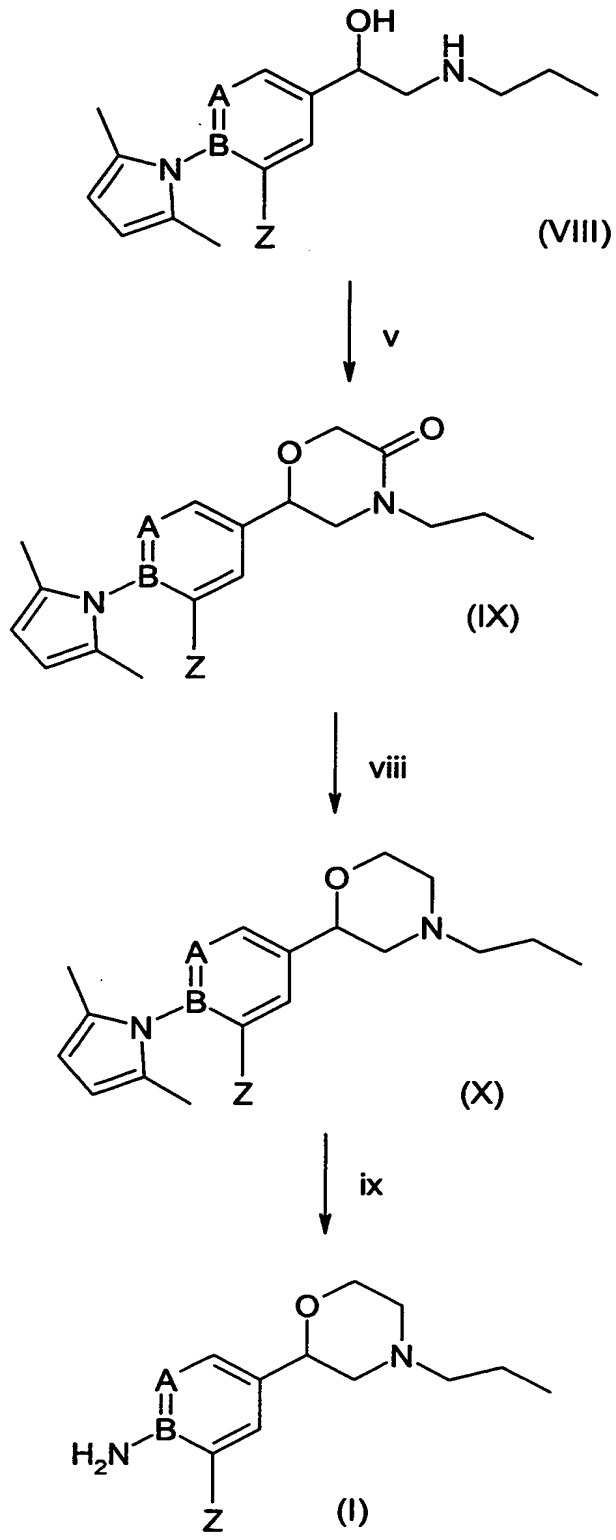
Compounds of formula (I) may be prepared by reacting compounds of formula (VI) with vi), reducing agents such as borane or lithium aluminium hydride. Typical conditions comprise 1.0 equivalents of amide VI, 1.2-3.0 equivalents of borane in THF at reflux.

The skilled man will appreciate that due to one of X, Y or Z being a hydroxy group, it will be necessary to protect the hydroxy group(s) with a suitable protecting group throughout the transformations of scheme 1, the remove the protecting group. Methods for deprotection of a phenol group depend on the protecting group. For examples of protection/deprotection methodology see "Protective groups in Organic synthesis", TW Greene and PGM Wutz. For example, where the hydroxy is protected as a methyl ether, deprotection conditions comprise refluxing in 48% aqueous HBr for 1-24 hours, or by stirring with borane tribromide in dichloromethane for 1-24 hours. Alternatively where the hydroxy is protected as a benxyl ether, deprotection conditions comprise hydrogenation with a palladium catalyst under a hydrogen atmosphere

Compounds of general formula (I) where one of A or B is N and X, Y and Z are as described herein, with the proviso that one of X, Y or Z is NH_2, may be prepared according to reaction scheme 2. Scheme is illustrated where B is C-Y and where Y is NH_2; the skilled man will understand that the alternative compounds are equally practicable.



(VII)



Scheme 2

Compounds of formula (VII) may be prepared using the process as described in JP2001048864.

Compounds of formula (VIII) may be prepared by reacting epoxide (VII) with vii), propylamine. Typical reaction conditions comprise stirring the epoxide with excess amine either neat or in dimethylsulphoxide.

Compounds of formula (IX) may be prepared by reacting compounds of formula (VIII) with v), chloroacetyl chloride in the presence of base such as triethylamine, sodium carbonate and potassium hydroxide. Typical conditions comprise 1.0 equivalents of amine (VIII), 1.2-2.0 equivalents of triethylamine in dichloromethane at 25°C, the crude reaction mixture is then dissolved in IPA with 1.2-3.0 equivalents of aqueous potassium hydroxide.

Compounds of formula (X) may be prepared by reacting compounds of formula (IX) with reducing agents such as lithium aluminium hydride. Typical conditions comprise 1.0 equivalents of amide (X), 1.2 equivalents of lithium aluminium hydride in THF at reflux.

Compounds of formula (I) may be prepared by ix), deprotection. Typical conditions comprise 1.0 equivalents of compound X and 5 equivalents of hydroxylamine hydrochloride in ethanol at reflux.

All of the above reactions and the preparations of novel starting materials using in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the Examples and Preparations hereto.

The compounds of the present invention have utility as selective D3 agonists in the treatment of disease states. There are a number of compounds with activity

as both D2 and D3 agonists; however the use of such compounds is associated with a large number of side effects including nausea, emesis, syncope, hypotension and bradycardia, some of which are a cause for serious concern.

It was previously held that the efficacy of the prior art compounds stemmed from their ability to agonise D2; however D2 agonism is implicated as a cause of the side effects detailed above.

The present invention provides a class of selective D3 agonists. Serendipitously, these have been found to be efficacious, whilst reducing the side effects associated with unselective prior art compounds.

Compounds of present invention are useful in treating sexual dysfunction, female sexual dysfunction, including hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder and sexual pain disorder; male erectile dysfunction, hypertension, neurodegeneration, psychiatric disorders, depression (e.g. depression in cancer patients, depression in Parkinson's patients, postmyocardial infarction depression, subsyndromal symptomatic depression, depression in infertile women, paediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, post partum depression and grumpy old man syndrome), generalized anxiety disorder, phobias (e.g. agoraphobia, social phobia and simple phobias), posttraumatic stress syndrome, avoidant personality disorder, premature ejaculation, eating disorders (e.g. anorexia nervosa and bulimia nervosa), obesity, chemical dependencies (e.g. addictions to alcohol, cocaine, heroin, phenobarbital, nicotine and benzodiazepines), cluster headache, migraine, pain, Alzheimer's disease, obsessive-compulsive disorder, panic disorder, memory disorders (e.g. dementia, amnestic disorders, and age-related cognitive decline (ARCD)), Parkinson's diseases (e.g. dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias), endocrine disorders (e.g. hyperprolactinaemia), vasospasm (particularly in the cerebral vasculature), cerebellar ataxia, gastrointestinal tract

disorders (involving changes in motility and secretion), negative symptoms of schizophrenia, premenstrual syndrome, fibromyalgia syndrome, stress incontinence, Tourette's syndrome, trichotillomania, kleptomania, male impotence, attention deficit hyperactivity disorder (ADHD), chronic paroxysmal hemicrania, headache (associated with vascular disorders), emotional lability, pathological crying, sleeping disorder (cataplexy) and shock.

Compounds of the present invention are particularly suitable for treating female sexual dysfunction, male erectile dysfunction, neurodegeneration, depression and psychiatric disorders.

The compounds of the present invention are useful in male sexual dysfunction, particularly male erectile dysfunction. Male erectile dysfunction (MED), otherwise known as male erectile disorder, is defined as:

> *"the inability to achieve and/or maintain a penile erection for satisfactory sexual performance" (NIH Consensus Development Panel on Impotence, 1993)"*

It has been estimated that the prevalence of erectile dysfunction (ED) of all degrees (minimal, moderate and complete impotence) is 52% in men 40 to 70 years old, with higher rates in those older than 70 (Melman *et al* 1999, J. Urology, 161, p5-11). The condition has a significant negative impact on the quality of life of the individual and their partner, often resulting in increased anxiety and tension which leads to depression and low self-esteem. Whereas two decades ago, MED was primarily considered to be a psychological disorder (Benet *et al* 1994 Comp. Ther., 20: 669-673), it is now known that for the majority of individuals there is an underlying organic cause. As a result, much progress has been made in identifying the mechanism of normal penile erection and the pathophysiologies of MED.

Penile erection is a haemodynamic event which is dependent upon the balance of contraction and relaxation of the corpus cavernosal smooth muscle and vasculature of the penis (Lerner *et al* 1993, J. Urology, 149, 1256-1255). Corpus cavernosal smooth muscle is also referred to herein as corporal smooth muscle or in the plural sense corpus cavernosa. Relaxation of the corpus cavernosal smooth muscle leads to an increased blood flow into the trabecular spaces of the corpus cavernosa, causing them to expand against the surrounding tunica and compress the draining veins. This produces a vast elevation in blood pressure which results in an erection (Naylor, 1998, J. Urology, 81, 424-431).

The changes that occur during the erectile process are complex and require a high degree of co-ordinated control involving the peripheral and central nervous systems, and the endocrine system (Naylor, 1998, J. Urology, 81, 424-431). Corporal smooth muscle contraction is modulated by sympathetic noradrenergic innervation via activation of postsynaptic α_1 adrenoceptors. MED may be associated with an increase in the endogenous smooth muscle tone of the corpus cavernosum. However, the process of corporal smooth muscle relaxation is mediated partly by non-adrenergic, non-cholinergic (NANC) neurotransmission. There are a number of other NANC neurotransmitters found in the penis, other than NO, such as calcitonin gene related peptide (CGRP) and vasoactive intestinal peptide (VIP). The main relaxing factor responsible for mediating this relaxation is nitric oxide (NO), which is synthesised from L-arginine by nitric oxide synthase (NOS) (Taub *et al* 1993 Urology, 42, 698-704). It is thought that reducing corporal smooth muscle tone may aid NO to induce relaxation of the corpus cavernosum. During sexual arousal in the male, NO is released from neurones and the endothelium and binds to and activates soluble guanylate cyclase (sGC) located in the smooth muscle cells and endothelium, leading to an elevation in intracellular cyclic guanosine 3',5'-monophosphate (cGMP) levels. This rise in cGMP leads to a relaxation of the corpus cavernosum due to a reduction in the intracellular calcium concentration ($[Ca^{2+}]_i$), via unknown mechanisms thought to involve

protein kinase G activation (possibly due to activation of Ca^{2+} pumps and Ca^{2+}-activated K^+ channels).

Multiple potential sites have been identified within the central nervous system for the modulation of sexual behaviour. The key neurotransmitters are thought to be serotonin, norepinephrine, oxytocin, nitric oxide and dopamine. By mimicking the actions of one of these key neurotransmitters sexual function may be adjusted. Dopamine D3 receptors are expressed almost exclusively in the limbic are of the brain, regions involved in the reward, emotional and cognitive processes.

Without being bound by any theory, it appears that "due to its role in the control of locomotor activity, the integrity of the nigrostriatal dopaminergic pathway is also essential for the display of copulatory behaviour. Somehow, more specific to sexual function, it is likely that dopamine can trigger penile erection by acting on oxytocinergic neurons located in the paraventricular nucleus of the hypothalamus, and perhaps on the pro-erectile sacral parasympathetic nucleus within the spinal cord". It now appears that the significant site is D3 and not as previously thought, D2.

In essence, D3 is an initiator of sexual behaviour.

Accordingly, the present invention provides for, the use of a compound of formula (I) in the preparation of a medicament for the treatment or prevention of erectile dysfunction.

Patients with mild to moderate MED should benefit from treatment with the compounds according to the present invention, and patients with severe MED may also respond. However, early investigations suggest that the responder rate of patients with mild, moderate and severe MED may be greater with a selective D3 agonist/PDE5 inhibitor combination. Mild, moderate and severe

MED will be terms known to the man skilled in the art, but guidance can be found in The Journal of Urology, vol. 151, 54-61 (Jan 1994).

Early investigations suggest the below mentioned MED patient groups should benefit from treatment with a selective D3 agonist and a PDE5i (or other combination set out hereinafter). These patient groups, which are described in more detail in Clinical Andrology vol. 23, no.4, p773-782 and chapter 3 of the book by I. Eardley and K. Sethia "Erectile Dysfunction-Current Investigation and Management, published by Mosby-Wolfe, are as follows: psychogenic, organic, vascular, endocrinologic, neurogenic, arteriogenic, drug-induced sexual dysfunction (lactogenic) and sexual dysfunction related to cavernosal factors, particularly venogenic causes.

Accordingly the present invention provides for the use of a compound of formula (I), (Ia) or (Ib) in the preparation of a medicament in combination with a PDE5 inhibitor for the treatment of erectile dysfunction.

Suitable PDE5 inhibitors are described herein.

The compounds of the present invention are useful in the treatment or prevention of female sexual dysfunction (FSD), particularly FSAD.

In accordance with the invention, FSD can be defined as the difficulty or inability of a woman to find satisfaction in sexual expression. FSD is a collective term for several diverse female sexual disorders (Leiblum, S.R. (1998) - Definition and classification of female sexual disorders. *Int. J. Impotence Res.*, **10**, S104-S106; Berman, J.R., Berman, L. & Goldstein, I. (1999) - Female sexual dysfunction: Incidence, pathophysiology, evaluations and treatment options. *Urology*, **54**, 385-391.). The woman may have lack of desire, difficulty with arousal or orgasm, pain with intercourse or a combination of these problems. Several types of disease, medications, injuries or psychological problems can cause FSD. Treatments in development are

targeted to treat specific subtypes of FSD, predominantly desire and arousal disorders.

The categories of FSD are best defined by contrasting them to the phases of normal female sexual response: desire, arousal and orgasm (Leiblum, S.R. (1998) - Definition and classification of female sexual disorders. *Int. J. Impotence Res.*, **10**, S104-S106). Desire or libido is the drive for sexual expression. Its manifestations often include sexual thoughts either when in the company of an interested partner or when exposed to other erotic stimuli. Arousal is the vascular response to sexual stimulation, an important component of which is genital engorgement and includes increased vaginal lubrication, elongation of the vagina and increased genital sensation/sensitivity. Orgasm is the release of sexual tension that has culminated during arousal.

Hence, FSD occurs when a woman has an inadequate or unsatisfactory response in any of these phases, usually desire, arousal or orgasm. FSD categories include hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorders and sexual pain disorders. Although the compounds of the invention will improve the genital response to sexual stimulation (as in female sexual arousal disorder), in doing so it may also improve the associated pain, distress and discomfort associated with intercourse and so treat other female sexual disorders.

Hypoactive sexual desire disorder is present if a woman has no or little desire to be sexual, and has no or few sexual thoughts or fantasies. This type of FSD can be caused by low testosterone levels, due either to natural menopause or to surgical menopause. Other causes include illness, medications, fatigue, depression and anxiety.

Female sexual arousal disorder (FSAD) is characterised by inadequate genital response to sexual stimulation. The genitalia do not undergo the engorgement that characterises normal sexual arousal. The vaginal walls are poorly

lubricated, so that intercourse is painful. Orgasms may be impeded. Arousal disorder can be caused by reduced oestrogen at menopause or after childbirth and during lactation, as well as by illnesses, with vascular components such as diabetes and atherosclerosis. Other causes result from treatment with diuretics, antihistamines, antidepressants e.g. selective serotonin re-uptake inhibitors (SSRIs) or antihypertensive agents.

Sexual pain disorders (includes dyspareunia and vaginismus) is characterised by pain resulting from penetration and may be caused by medications which reduce lubrication, endometriosis, pelvic inflammatory disease, inflammatory bowel disease or urinary tract problems.

As previously discussed, D3 is thought to be an initiator of sexual behaviour. The clitoris is considered to be a homologue of the penis (Levin, R.J. (1991), *Exp. Clin. Endocrinol.*, **98**, 61-69); the same mechanism that provides provides an erectile response in the male produces an increase in genital blood flow in the female with an associated effect upon FSD. In addition there are changes in proceptivity and receptivity.

Thus, in accordance with a preferred aspect of the invention, there is provided use of a compound of formula (I), (Ia) or (Ib) in the preparation of a medicament for the treatment or prophylaxis of female sexual dysfunction, more particularly hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder and sexual pain disorder.

Preferably the compounds of formula (I) are useful in the treatment or prophylaxis of sexual arousal disorder, orgasmic disorder, and hypoactive sexual desire disorder, and most preferably in the treatment or prophylaxis of sexual arousal disorder.

In a preferred embodiment the compounds of formula (I), (Ia) and (Ib) are useful in the treatment of a subject with female sexual arousal disorder and concomitant hypoactive sexual desire disorder.

The Diagnostic and Statistical Manual (DSM) IV of the American Psychiatric Association defines Female Sexual Arousal Disorder (FSAD) as being:

"... *a persistent or recurrent inability to attain or to maintain until completion of the sexual activity adequate lubrication-swelling response of sexual excitement. The disturbance must cause marked distress or interpersonal difficulty.* ...".

The arousal response consists of vasocongestion in the pelvis, vaginal lubrication and expansion and swelling of the external genitalia. The disturbance causes marked distress and/or interpersonal difficulty.

FSAD is a highly prevalent sexual disorder affecting pre-, peri- and post-menopausal (± hormone replacement therapy (HRT)) women. It is associated with concomitant disorders such as depression, cardiovascular diseases, diabetes and urogenital (UG) disorders.

The primary consequences of FSAD are lack of engorgement/swelling, lack of lubrication and lack of pleasurable genital sensation. The secondary consequences of FSAD are reduced sexual desire, pain during intercourse and difficulty in achieving an orgasm.

It has recently been hypothesised that there is a vascular basis for at least a proportion of patients with symptoms of FSAD (Goldstein *et al.*, Int. J. Impot. Res., 10, S84-S90,1998) with animal data supporting this view (Park *et al.*, Int. J. Impot. Res., 9, 27-37, 1997).

R.J. Levin teaches us that because "... *male and female genitalia develop embryologically from the common tissue anlagen, [that] male and female genital*

structures are argued to be homologues of one another. Thus the clitoris is the penile homologue and the labia homologues of the scrotal sac. ..." (Levin, R.J. (1991), *Exp. Clin. Endocrinol.*, **98**, 61-69).

Drug candidates for treating FSAD, which are under investigation for efficacy, are primarily erectile dysfunction therapies that promote circulation to male genitalia. .

The compounds of the present invention are advantageous by providing a means for restoring a normal sexual arousal response - namely increased genital blood flow leading to vaginal, clitoral and labial engorgement. This will result in increased vaginal lubrication via plasma transudation, increased vaginal compliance and increased genital sensitivity. Hence, the present invention provides a means to restore, or potentiate, the normal sexual arousal response.

Thus, in accordance with a preferred aspect of the invention, there is provided use of a compound of formula (I), (Ia) or (Ib) in the preparation of a medicament for the treatment or prophylaxis of female sexual arousal disorder.

By female genitalia herein we mean: "The genital organs consist of an internal and external group. The internal organs are situated within the pelvis and consist of ovaries, the uterine tubes, uterus and the vagina. The external organs are superficial to the urogenital diaphragm and below the pelvic arch. They comprise the mons pubis, the labia majora and minora pudendi, the clitoris, the vestibule, the bulb of the vestibule, and the greater vestibular glands" (Gray's Anatomy, C.D. Clemente, 13th American Edition).

The compounds of the invention find application in the following sub-populations of patients with FSD: the young, the elderly, pre-menopausal, peri-

menopausal, post-menopausal women with or without hormone replacement therapy.

The compounds of the invention find application in patients with FSD arising from:-

i) Vasculogenic etiologies e.g. cardiovascular or atherosclerotic diseases, hypercholesterolemia, cigarette smoking, diabetes, hypertension, radiation and perineal trauma, traumatic injury to the iliohypogastric pudendal vascular system.

ii) Neurogenic etiologies such as spinal cord injuries or diseases of the central nervous system including multiple sclerosis, diabetes, Parkinsonism, cerebrovascular accidents, peripheral neuropathies, trauma or radical pelvic surgery.

iii) Hormonal/endocrine etiologies such as dysfunction of the hypothalamic/pituitary/gonadal axis, or dysfunction of the ovaries, dysfunction of the pancreas, surgical or medical castration, androgen deficiency, high circulating levels of prolactin e.g. hyperprolactinemia, natural menopause, premature ovarian failure, hyper and hypothyroidism.

iv) Psychogenic etiologies such as depression, obsessive compulsive disorder, anxiety disorder, postnatal depression/"Baby Blues", emotional and relational issues, performance anxiety, marital discord, dysfunctional attitudes, sexual phobias, religious inhibition or a traumatic past experiences.

v) Drug-induced sexual dysfunction resulting from therapy with selective serotonin reuptake inhibitors (SSRis) and other antidepressant therapies (tricyclics and major tranquillizers), anti-hypertensive therapies, sympatholytic drugs, chronic oral contraceptive pill therapy.

The Compounds of the present invention are also useful in the treatment of depression.

Dopamine D3 receptors are expressed almost exclusively in the limbic area of the brain, regions involved in reward, emotional and cognitive processes. Chronic treatment with several classes of antidepressants are known to increase the expression of D3 in the limbic area, and antidepressant effects of desipramine can be blocked by sulpride (D2/D3 antagonist) when injected to nucleus accumbens (area rich in D3) but not caudate-putamen (area rich in dopamine D2 receptors). In addition, antidepressant effects were observed preclinical models of depression and in patients treated with pramipexole, a D3-preferring agonist. The available information suggests that D3 receptors mediate the anti-depressant activity and that selective D3 receptor agonists represent a new class of antidepressant drugs. Since antidepressants are known to be effective in other psychiatric disorders, D3 agonists would have the potential to treat psychiatric diseases.

The present invention provides for the use of a selective D3 agonist in the preparation of a medicament for the treatment of depression and psychiatric diseases.

Preferably said D3 agonist exhibit a functional potency at D3 receptor expressed as an EC50, lower than 1000nm, more preferably lower than 100nm, yet more preferably lower than 50nm, most preferably lower than 10nm.

Preferably said D3 agonist has a selectivity for D3 over D2, wherein said dopamine D3 receptor agonist is at least about 15-times, preferably at least about 27-times, more preferably at least about 30-times, most preferably at least about 100-times more functionally selective for a dopamine D3 receptor as compared with a dopamine D2 receptor

Suitable conditions include depression (e.g. depression in cancer patients, depression in Parkinson's patients, postmyocardial infarction depression, subsyndromal symptomatic depression, depression in infertile women, paediatric depression, major depression, single episode depression, recurrent

depression, child abuse induced depression, post partum depression and grumpy old man syndrome), generalized anxiety disorder, phobias (e.g. agoraphobia, social phobia and simple phobias), posttraumatic stress syndrome, avoidant personality disorder, eating disorders (e.g. anorexia nervosa and bulimia nervosa), obesity, chemical dependencies (e.g. addictions to alcohol, cocaine, heroin, phenobarbital, nicotine and benzodiazepines), Alzheimer's disease, obsessive-compulsive disorder, panic disorder, memory disorders (e.g. dementia, amnestic disorders, and age-related cognitive decline (ARCD)), Parkinson's diseases (e.g. dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias), endocrine disorders (e.g. hyperprolactinaemia), vasospasm (particularly in the cerebral vasculature), cerebellar ataxia, negative symptoms of schizophrenia, stress incontinence, Tourette's syndrome, trichotillomania, kleptomania, attention deficit hyperactivity disorder (ADHD), chronic paroxysmal hemicrania, emotional lability, pathological crying, sleeping disorder (cataplexy) and shock.

In a preferred embodiment, the present invention provides for the use of a compound of formula (I), (Ia) and (Ib) in the preparation of a medicament for the treatment of depression or psychiatric disorders.

Suitable depressive conditions and psychiatric disorders are described above.

The compounds of the present invention also have utility in the treatment of neurodegeneration; sources of neurodegeneration include neurotoxin poisoning; vision loss caused by neurodegeneration of the visual pathway, such as by a stroke in the visual pathway eg in retina, optic nerve and/or occipital lobe; epileptic seizures; and from impairment of glucose and/or oxygen supply to the brain.

Accordingly the present invention provides for the use of a selective D3 agonist in the preparation of a medicament for the treatment of neurodegeneration.

Preferably said D3 agonist exhibit a functional potency at D3 receptor expressed as an EC50, lower than 1000nm, more preferably lower than 100nm, yet more preferably lower than 50nm, most preferably lower than 10nm.

Preferably said D3 agonist has a selectivity for D3 over D2, wherein said dopamine D3 receptor agonist is at least about 15-times, preferably at least about 27-times, more preferably at least about 30-times, most preferably at least about 100-times more functionally selective for a dopamine D3 receptor as compared with a dopamine D2 receptor

In a preferred embodiment, the D3 agonist is a compound of formula (I), (Ia) or (Ib)

In addition to their role in treating Sexual dysfunction, depression, neurodegeneration and psychiatric disorders, the compounds of the present invention are likely to be efficacious in a number of additional indications.

Accordingly, the present invention provides for the use of compounds of formula (I), (Ia) or (Ib) in the preparation of a medicament for the treatment of hypertension, premature ejaculation, obesity, cluster headache, migraine, pain, endocrine disorders (e.g. hyperprolactinaemia), vasospasm (particularly in the cerebral vasculature), cerebellar ataxia, gastrointestinal tract disorders (involving changes in motility and secretion), premenstrual syndrome, fibromyalgia syndrome, stress incontinence, trichotillomania and chronic paroxysmal hemicrania, headache (associated with vascular disorders).

<u>D3/D2 AGONIST BIND ASSAY</u>

Gonazalez *et al* (Eup. J Pharmacology 272 (1995) R1-R3) discloses an assay for determining the binding capability of a compound at D3 and/or D2 dopamine receptors and thus the binding selectivity of such compounds. This assay is, thus, herein referred to as a binding assay.

D3/D2 AGONIST FUNCTIONAL ASSAY

A suitable assay for determining functionally the activity of a compound at D3 and/or D2 dopamine receptors is detailed hereinbelow.

Compounds are evaluated as agonists or antagonists at the dopamine D2 and D3 receptors by looking at cAMP levels in a GH4C1 and CHO cell-line expressing the human D2 and D3 receptors, respectively.

EXPERIMENTAL PROCEDURE

MATERIALS

- Cell culture media:

HD2LhD$_2$LGH4C1 Medium	hD$_3$CHO Medium
Hams F-10 (Sigma N6013)	DMEM, high glucose (Sigma D5671)
2mM L-Glutamine (Sigma G7513)	2mM L-Glutamine (Sigma G7513)
10% FBS (Gibco 10106-169)	10% dialyzed FBS (Sigma F0392)
700µg/ml Geneticin (Gibco 10131-019)	20nM Methotrexate hydrate (Sigma M8407)

Two adherent cell lines expressing cloned human dopamine receptors are:

hD$_2$LGH4C1 - rat pituitary cells expressing the human dopamine 2 long receptor; and

hD$_3$CHO - Chinese hamster ovary cells deficient in dihydrofolate reductase gene which express the human dopamine D3 receptor.

Media required for their growth is made up fresh every week as below and filtered through a 0.22μM filter before use. Media stored at 4°C and warmed to 37°C for addition to the cells.

- Cell Dissociation Solution:

(Sigma C-5914) 10-15ml used to harvest cells from 225cm^2 flask (37°C 5 min for hD2LGH4C1 cells and 10 minutes for hD3CHO cells).

- KRH buffer:

KRH is prepared as follows:

KH_2PO_4	(BDH – 1025034B)	1.2mM	163mg/l
NaCl	(Fisher - S/3160/60)	1.45M	8.47g/l
KCl	(Sigma – P-9333)	5mM	373mg/l
$MgSO_4$	(BDH – 101514Y)	1.2mM	296mg/l
$CaCl_2$	(Sigma – C-5080)	1mM	147mg/l
Hepes	(Sigma – H-7523)	25mM	5.96g/l
Glucose	(BDH – 101176K)	5mM	0.9g/l

Made up to 1 litre with distilled water and pH adjusted to pH 7.4 at room temperature. Stored for up to 1 week at 4°C.

- 3-isobutyl-1-methylxanthine (IBMX):

(Sigma I7018) Dissolved to a concentration of 100mM in DMSO. 10x assay stock of 1mM made by carrying out a 1:100 dilution in KRH buffer. 20μl added to a final assay volume of 200μl, giving a final assay concentration of 100μM/well.

Forskolin:

(Calbiochem 344273) Dissolved to a concentration of 10mM in water. (This stock is stored at +4°C). 10x assay stock of 100µM and 200µM made by carrying out a 100 and 50 fold dilution in KRH buffer. 20µl added to a final assay volume of 200µl, giving a final assay concentration of 10µM for the D2 cells and 20µM for the D3 cells.

- Test compounds:

Dissolved to a concentration of 10mM in 100 % DMSO and diluted in KRH buffer to give the top concentration of 100µM/well in 1%DMSO/KRH (10µM/well in 0.1%DMSO/KRH in assay). Further dilutions are made in 1%DMSO/KRH (10X assay concentration): 10µM, 1µM, 100nM, 10nM, 1nM, 0.1nM, 0.01nM and 0.001nM. 20µl added to a final assay volume of 200µl, giving the following final assay concentrations: 1µM, 100nM, 10nM, 1nM, 0.1nM, 0.01nM and 0.001nM Compounds are normally assayed from 1e-5 to 1e-12.
The following compounds are always included in the assay:

Apomorphine
Assayed from 1e-5 to 1e-12
Full agonist

- cAMP Enzymeimmunoassay:

All materials are supplied by Amersham Pharmacia Biotech cAMP EIA kit (RPN 225) unless otherwise stated.

- Microtitre plate:

96 well plate coated with donkey anti-rabbit IgG.

- Assay buffer:

0.05M sodium acetate buffer, pH 5.8 containing 0.02% bovine serum albumin and 0.01% preservative upon dilution. The contents of this bottle are transferred to a graduated cylinder using 3 x 15ml distilled water washes. The final volume is then adjusted to 500ml.

- cAMP standard (for non-acetylation assay):

cAMP at 3200fmol/ml upon reconstitution. Standard is dissolved in 2ml lysis reagent 1B (see below) for use.

- Antibody:

Rabbit anti-cAMP. Antibody is dissolved in 11ml lysis reagent 2B (see below) for use.

- Peroxidase conjugate:

cAMP-horseradish peroxidase. Peroxidase conjugate is dissolved in 11ml assay buffer for use.

- Wash buffer:

0.01M phosphate buffer, pH7.5 containing 0.05% Tween 20 on dilution. The contents of this bottle are transferred to a graduated cylinder using 3 x 15ml distilled water washes. The final volume is then adjusted to 500ml.

- TMB substrate:

3,3',5,5'-tetramethylbenzidine (TMB)/hydrogen peroxide, in 20% (v/v) dimethylformamide.

- Lysis reagent 1:

Dodecyltrimethlyammonium bromide (25mg/ml on reconstituion). The powder is transferred to a 100ml graduated cylinder using 3 x 15ml assay buffer. The volume is adjusted to 60ml and stirred until dissolved. The final volume is then made up to 80ml with assay buffer.

- Lysis reagent 1B:

5ml of lysis reagent 1 is diluted to 50ml with assay buffer.

- Lysis reagent 2:

Solid, 5g. Contains no chemicals classified as hazardous. The powder is transferred to a 100ml graduated cylinder using 3 x 15ml assay buffer. The volume is adjusted to 80ml and stirred until dissolved. The final volume is then made up to 100ml with assay buffer.

- Lysis reagent 2B:

10ml of lysis reagent 2 is diluted to 40ml with assay buffer.

- Sulphuric acid (1M):

1M Sulphuric acid is prepared from an 18M stock (BDH). 11ml of acid is added to 189ml of distilled water.

SPECIFIC EQUIPMENT

Spectroscophometric plate reader (Spectra max 190)

Microtitre plate shaker/incubator (Wesbart)

METHODS

RESUSCITATION OF FROZEN AMPOULES:

Remove ampoules from liquid nitrogen and allow them to equilibrate for 2 minutes as trapped gas or liquid may cause the ampoule may expand rapidly and explode. They can also be placed at minus 20°C before thawing.

Thaw ampoules quickly and completely at 37°C in a water bath.

Transfer the contents to a 15ml tube carefully. Slowly add 2ml of media and then another 8 ml.

Transfer cell suspension to a T25 flask and incubate for 24h at 37°C, 5% CO_2. N.B. hD_3CHO cells can be placed straight into a T225 flask as they are fast growing cells, the amount of medium required is 50ml.

Cell harvesting and splitting:

Generally, cells are split on a Monday and Wednesday in order to perform assays on Tuesday and Thursday. Cells may also be split on Friday if too confluent to leave over the weekend. It is very important not to let the hD_3CHO cells grow beyond 80% confluency as they cannot be recovered once grown past this point.

Cells are grown in T225 flasks (Jumbos). Every component added to th cells must be warmed to 37°C before use.

C ll harv st:

Growth media removed from flasks and cells washed twice with warm PBS (Gibco. 14040-091) and removed.

1. Approximately 10ml of cell dissociation buffer (Sigma C5914) added to cells and placed in incubator for approx. 5 min. (D_3 cells adhere more strongly to the flask than D_2s, therefore D_3 cells may require longer to dislodge)

2. Flasks given a sharp tap when removed from the incubator to dislodge any remaining cells from the bottom.

3. Approx. 10ml of full medium added to the cells and used to wash the sides of the flask. Cells are centrifuged for 5min at 1000rpm to pellet the cells.

4. Media is discarded and 10ml of fresh medium used to resuspend the cells. 100µl removed and combined with 100µl of trypan blue (Sigma T8154) for counting.

Split ratios:

hD_2LGH4C1 split between 1:3 to 1:6
hD_3CHO split between 1:5 to 1:10 (faster growing of the two cell lines)

Seeding for assay:

Require 50,000 cells/200µl/well equal to 2.5×10^5 cells/ml. Dilute cells to 2.5×10^5 cells/ml and add 200µl to wells in a tissue culture 96 well plate. Leave all cells at 37°C, 5% CO_2.

Cryopreservation of cell lines:

It is a good idea to create a cell bank of your own cells to resuscitate for further use.

Cells are harvested in the same manner as before.

Cells are counted

Freeze medium contains full medium plus 10% DMSO, cells resuspended to give between 2 to 4 x 10^6 cells/ml. Cell suspension is divided into 1ml aliquots.

The cells are frozen down between 1°C to 3°C using 'Mr Frosty' in the minus 80°C freezer overnight before being transferred to a gaseous phase nitrogen storage vessel.

It is advisable to test the cell viability by thawing one ampoule after freezing. Viabilities below 70% may cause problems on recovery due to low cell numbers and the presence of debris.

Measurement of intracellular cAMP levels in cells:

Cells are plated at 50,000 cells/well into sterile 96-well plates in cell culture medium (see section 3) at a final volume of 200µl/well the previous day and incubated at 37°C, 5%CO_2 O/N.

KRH buffer is made up as section 1 and warmed to 37°C.

IBMX, Forskolin and test compounds are made up and diluted as section 1.

Cells are washed once with 200µl KRH buffer.

The following are added to each well:

HD2LhD$_2$GH4C1 cells	**hD$_3$CHO cells**
120µl KRH buffer	120µl KRH buffer
20µl IMBX (100µM/well)	20µl IMBX (100µM/well)
20µl Forskolin (10µM/well)	20µl Forskolin (20µM/well)
20µl Agonist	20µl Agonist
20µl Antagonist or 1% DMSO	20µl Antagonist or 1% DMSO

Controls:

Forskolin only	Blank	DMSO CONTROL	Antagonist control
160µl KRH buffer	200µl KRH	120µl KRH buffer	120µl KRH buffer
20µl IMBX (100µM/well)		20µl IMBX (100µM/well)	20µl IMBX (100µM/well)
20µl Forskolin (10µM/well)		20µl Forskolin (10µM/well)	20µl Forskolin (10µM/well)
		40µl 1% DMSO	20µl 1% DMSO
			20µl Antagonist

The plates are shaken at 37°C for 45mins.

After 45 min the assay mixture is aspirated and 200µl of lysis reagent 1B added to the cells.

Cells are shaken for 20 min before further lysing by repeated pipetting (~20 times/well).

<u>cAMP Enzymeimmunoassay:</u>

Stock reagents equilibrated to room temperature and working solutions prepared (as described above).

cAMP standards prepared in eppendorf tubes labelled 12.5, 25, 50, 100, 200, 400, 800, 1600 and 3200 fmol. 0.5ml of lysis reagent 1B is added to each tube. 0.5ml of the diluted standard is added to the 3200fmol tube. The tube is vortexed and 0.5ml added to the 1600fmol tube. This is continued to give the other dilutions.

20µl (hD_2) and 100µl (hD_3) of each cell lysate is transferred to the EIA plate and for the hD2 sample made up to 100µl with lysis reagent 1B. No further addition is added to the hD3 sample. 100µl of each standard and of the original standard is placed in duplicate into the plate. The following controls are set up:

zero standard: 100µl lysis reagent 1B

NSB: 100µl lysis reagent 1B and 2B

Blank: no additions

See appendix 2 for typical plate layout.

100µl of antibody is added to all wells except for blank and NSB wells before incubating for 2 hours at 4°C.

After incubation, 50µl of peroxidase conjugate is added to all wells except for the blank wells and incubated for a further hour at 4°C.

Plates are emptied by blotting onto absorbent paper and washed 4 times with 400µl of wash buffer. 150µl of TMB substrate is then added to each well.

Plates are shaken at room temperature for 30 min before the addition of 100µl of 1M sulphuric acid into all wells.

The optical density is read on Spectramax 190 at 450nM within 30minutes.

CALCULATIONS

Calculations are carried out using a combination of Excel and Origin templates.

The standard curve is generated by plotting percentage of control OD data (y axis) against log cAMP (x-axis) mol/well in Excel. Standard curve is constrained through 0 and 100.

From standard curve, cAMP predictions are made for each sample well using the variables generated from the standard curve.

Formula for predicting a dose given a response from a sigmoid curve.

$$x = c\left(\frac{y - a}{d - y}\right)^{1/b}$$

where:- a = lower asymptote
b = hill slope
c = IC_{50}
d = upper asymptote

- cAMP predictions are made for each OD reading and expressed as a percentage of Dmso control.

Plotting Log concentration of compound (x-axis) against percentage control response (y-axis), a sigmoidal dose response curve can be constructed from which an EC_{50} concentration can be obtained.

The compounds of the present invention all exhibit a functional potency at D3 receptor expressed as an EC50, lower than 1000nm and a 10 fold selectivity for D3 over D2.

Compound of example 8 has a functional potency at D3 receptor expressed as an EC50, of 7.3nm and a 681 fold selectivity for D3 over D2.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

Suitabl auxiliary active agents for use in the combinations of the present invention include:

1) Naturally occurring or synthetic prostaglandins or esters thereof. Suitable prostaglandins for use herein include compounds such as alprostadil, prostaglandin E_1,prostaglandin E_0, 13, 14 - dihydroprosta glandin E_1, prostaglandin E_2, eprostinol, natural synthetic and semi-synthetic prostaglandins and derivatives thereof including those described in WO-00033825 and/or US 6,037,346 issued on 14th March 2000 all incorporated herein by reference, PGE_0, PGE_1, PGA_1, PGB_1, $PGF_1\alpha$, 19-hydroxy PGA_1, 19-hydroxy - PGB_1, PGE_2, PGB_2, 19-hydroxy-PGA_2, 19-hydroxy-PGB_2, $PGE_3\alpha$, carboprost tromethamine dinoprost, tromethamine, dinoprostone, lipo prost, gemeprost, metenoprost, sulprostune, tiaprost and moxisylate;

2) α - adrenergic receptor antagonist compounds also known as α - adrenoceptors or α-receptors or α-blockers. Suitable compounds for use herein include: the α-adrenergic receptor blockers as described in PCT application WO99/30697 published on 14th June 1998, the disclosures of which relating to α-adrenergic receptors are incorporated herein by reference and include, selective α_1-adrenoceptor or α_2-adrenoceptor blockers and non-selective adrenoceptor blockers, suitable α_1-adrenoceptor blockers include: phentolamine, phentolamine mesylate, trazodone, alfuzosin, indoramin, naftopidil, tamsulosin, dapiprazole, phenoxybenzamine, idazoxan, efaraxan, yohimbine, rauwolfa alkaloids, Recordati 15/2739, SNAP 1069, SNAP 5089, RS17053, SL 89.0591, doxazosin, terazosin, abanoquil and prazosin; α_2-blocker blockers from US 6,037,346 [14th March 2000] dibenamine, tolazoline, trimazosin and dibenamine; α-adrenergic receptors as described in US patents: 4,188,390; 4,026,894; 3,511,836; 4,315,007; 3,527,761; 3,997,666; 2,503,059; 4,703,063; 3,381,009; 4,252,721 and 2,599,000 each of which is incorporated herein by reference; α_2-Adrenoceptor blockers include:

clonidine, papaverine, papaverine hydrochloride, optionally in the presence of a cariotonic agent such as pirxamine;

3) NO-donor (NO-agonist) compounds. Suitable NO-donor compounds for use herein include organic nitrates, such as mono- di or tri-nitrates or organic nitrate esters including glyceryl trinitrate (also known as nitroglycerin), isosorbide 5-mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, sodium nitroprusside (SNP), 3-morpholinosydnonimine molsidomine, S-nitroso- N-acetyl penicilliamine (SNAP) S-nitroso-N-glutathione (SNO-GLU), N-hydroxy - L-arginine, amylnitrate, linsidomine, linsidomine chlorohydrate, (SIN-1) S-nitroso - N-cysteine, diazenium diolates,(NONOates), 1,5-pentanedinitrate, L-arginene, ginseng, zizphi fructus, molsidomine, Re – 2047, nitrosylated maxisylyte derivatives such as NMI-678-11 and NMI-937 as described in published PCT application WO 0012075;

4) Potassium channel openers or modulators. Suitable potassium channel openers/modulators for use herein include nicorandil, cromokalim, levcromakalim, lemakalim, pinacidil, cliazoxide, minoxidil, charybdotoxin, glyburide, 4-amini pyridine, $BaCl_2$;

5) Vasodilator agents. Suitable vasodilator agents for use herein include nimodepine, pinacidil, cyclandelate, isoxsuprine, chloroprumazine, halo peridol, Rec 15/2739, trazodone;

6) Thromboxane A2 agonists;

7) CNS active agents;

8) Ergot alkoloids; Suitable ergot alkaloids are described in US patent 6,037,346 issued on 14th March 2000 and include acetergamine, brazergoline, bromerguride, cianergoline, delorgotrile, disulergine,

ergonovine maleate, ergotamine tartrate, etisulergine, lergotrile, lysergide, mesulergine, metergoline, metergotamine, nicergoline, pergolide, propisergide, proterguride and terguride;

9) Compounds which modulate the action of natruretic factors in particular atrial naturetic factor (also known as atrial naturetic peptide), B type and C type naturetic factors such as inhibitors or neutral endopeptidase;

10) Compounds which inhibit angiotensin-converting enzyme such as enapril, and combined inhibitors of angiotensin-converting enzyme and neutral endopeptidase such as omapatrilat.

11) Angiotensin receptor antagonists such as losartan;

12) Substrates for NO-synthase, such as L-arginine;

13) Calcium channel blockers such as amlodipine;

14) Antagonists of endothelin receptors and inhibitors or endothelin-converting enzyme;

15) Cholesterol lowering agents such as statins (e.g. atorvastatin/ Lipitor- trade mark) and fibrates;

16) Antiplatelet and antithrombotic agents, e.g. tPA, uPA, warfarin, hirudin and other thrombin inhibitors, heparin, thromboplastin activating factor inhibitors;

17) Insulin sensitising agents such as rezulin and hypoglycaemic agents such as glipizide;

18) L-DOPA or carbidopa;

19) Acetylcholinesterase inhibitors such as donezipil;

20) Steroidal or non-steroidal anti-inflammatory agents;

21) Estrogen receptor modulators and/or estrogen agonists and/or estrogen antagonists, preferably raloxifene or lasofoxifene, (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol and pharmaceutically acceptable salts thereof the preparation of which is detailed in WO 96/21656;

23) A PDE inhibitor, more particularly a PDE 2, 3, 4, 5, 7 or 8 inhibitor, preferably PDE2 or PDE5 inhibitor and most preferably a PDE5 inhibitor (see hereinafter), said inhibitors preferably having an IC50 against the respective enzyme of less than 100nM (with the proviso that PDE 3 and 4 inhibitors are only administered topically or by injection to the penis);

22) Vasoactive intestinal protein (VIP), VIP mimetic, VIP analogue, more particularly mediated by one or more of the VIP receptor subtypes VPAC1,VPAC or PACAP (pituitory adenylate cyclase activating peptide), one or more of a VIP receptor agonist or a VIP analogue (e.g. Ro-125-1553) or a VIP fragment, one or more of a α-adrenoceptor antagonist with VIP combination (e.g. Invicorp, Aviptadil);

23) A melanocortin receptor agonist or modulator or melanocortin enhance, such as melanotan II, PT-14, PT-141 or compounds claimed in WO-09964002, WO-00074679, WO-09955679, WO-00105401, WO-00058361, WO-00114879, WO-00113112, WO-09954358;

24) A serotonin receptor agonist, antagonist or modulator, more particularly agonists, antagonists or modulators for 5HT1A (including VML 670), 5HT2A, 5HT2C, 5HT3 and/or 5HT6 receptors, including those described in WO-09902159, WO-00002550 and/or WO-00028993;

25) A testosterone replacement agent (including dehydroandrostendione), testosternone (Tostrelle), dihydrotestosterone or a testosterone implant;

26) Estrogen, estrogen and medroxyprogesterone or medroxyprogesterone acetate (MPA) (i.e. as a combination), or estrogen and methyl testosterone hormone replacement therapy agent (e.g. HRT especially Premarin, Cenestin, Oestrofeminal, Equin, Estrace, Estrofem, Elleste Solo, Estring, Eastraderm TTS, Eastraderm Matrix, Dermestril, Premphase, Preempro, Prempak, Premique, Estratest, Estratest HS, Tibolone);

27) A modulator of transporters for noradrenaline, dopamine and/or serotonin, such as bupropion, GW-320659;

28) A purinergic receptor agonist and/or modulator;

29) A neurokinin (NK) receptor antagonist, including those described in WO-09964008;

30) An opioid receptor agonist, antagonist or modulator, preferably agonists for the ORL-1 receptor;

31) An agonist or modulator for oxytocin/vasopressin receptors, preferably a selective oxytocin agonist or modulator;

32)Modulators of cannabinoid receptors;

33) A SEP inhibitor (SEPi), for instance a SEPi having an IC_{50} at less than 100 nanomolar, more preferably, at less than 50 nanomolar.

Preferably, the SEP inhibitors according to the present invention have

greater than 30-fold, more preferably greater than 50-fold selectivity for SEP over neutral endopeptidase NEP EC 3.4.24.11 and angiotensin converting enzyme (ACE). Preferably the SEPi also has a greater than 100-fold selectivity over endothelin converting enzyme (ECE).

By cross reference herein to compounds contained in patents and patent applications which can be used in accordance with invention, we mean the therapeutically active compounds as defined in the claims (in particular of claim 1) and the specific examples (all of which is incorporated herein by reference).

If a combination of active agents is administered, then they may be administered simultaneously, separately or sequentially.

Auxiliary Agents - PDE5 Inhibitors

The suitability of any particular cGMP PDE5 inhibitor can be readily determined by evaluation of its potency and selectivity using literature methods followed by evaluation of its toxicity, absorption, metabolism, pharmacokinetics, etc in accordance with standard pharmaceutical practice.

IC50 values for the cGMP PDE5 inhibitors may be determined using the PDE5 assay (see hereinbelow).

Preferably the cGMP PDE5 inhibitors used in the pharmaceutical combinations according to the present invention are selective for the PDE5 enzyme. Preferably (when used orally) they are selective over PDE3, more preferably over PDE3 and PDE4. Preferably (when oral), the cGMP PDE5 inhibitors of the invention have a selectivity ratio greater than 100 more preferably greater than 300, over PDE3 and more preferably over PDE3 and PDE4.

Selectivity ratios may readily be determined by the skilled person. IC50 values for the PDE3 and PDE4 enzyme may be determined using established

literature methodology, see S A Ballard *et al*, Journal of Urology, 1998, vol. 159, pages 2164-2171 and as detailed herein after.

Suitable cGMP PDE5 inhibitors for the use according to the present invention include:

the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in EP-A-0463756; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in EP-A-0526004; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 93/06104; the isomeric pyrazolo [3,4-d]pyrimidin-4-ones disclosed in published international patent application WO 93/07149; the quinazolin-4-ones disclosed in published international patent application WO 93/12095; the pyrido [3,2-d]pyrimidin-4-ones disclosed in published international patent application WO 94/05661; the purin-6-ones disclosed in published international patent application WO 94/00453; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 98/49166; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 99/54333; the pyrazolo [4,3-d]pyrimidin-4-ones disclosed in EP-A-0995751; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 00/24745; the pyrazolo [4,3-d]pyrimidin-4-ones disclosed in EP-A-0995750; the compounds disclosed in published international application WO95/19978; the compounds disclosed in published international application WO 99/24433 and the compounds disclosed in published international application WO 93/07124. The pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international application WO 01/27112; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international application WO 01/27113; the compounds disclosed in EP-A-1092718 and the compounds disclosed in EP-A-1092719.

Further suitable PDE5 inhibitors for the use according to the present inv ntion include:

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil) also known as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulphonyl]-4-methylpiperazine (see EP-A-0463756); 5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see EP-A-0526004); 3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO98/49166); 3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO99/54333); (+)-3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1(R)-methylethoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, also known as 3-ethyl-5-{5-[4-ethylpiperazin-1-ylsulphonyl]-2-([(1R)-2-methoxy-1-methylethyl]oxy)pyridin-3-yl}-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one (see WO99/54333); 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, also known as 1-{6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-3-pyridylsulphonyl}-4-ethylpiperazine (see WO 01/27113, Example 8); 5-[2-*iso*-Butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(1-methylpiperidin-4-yl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO 01/27113, Example 15); 5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-phenyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO 01/27113, Example 66); 5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (see WO 01/27112, Example 124); 5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (see WO 01/27112, Example 132);

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl) -pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (IC-351), i.e. the compound of examples 78 and 95 of published international application WO95/19978, as well as the compound of examples 1, 3, 7 and 8; 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil) also known as 1-[[3-(3,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f]-as-triazin-2-yl)-4-ethoxyphenyl]sulphonyl]-4-ethylpiperazine, i.e. the compound of examples 20, 19, 337 and 336 of published international application WO99/24433; and the compound of example 11 of published international application WO93/07124 (EISAI); and compounds 3 and 14 from Rotella D P, *J. Med. Chem.*, 2000, 43, 1257.

Still other suitable PDE5 inhibitors include:

4-bromo-5-(pyridylmethylamino)-6-[3-(4-chlorophenyl)-propoxy]-3(2H)pyridazinone; 1-[4-[(1,3-benzodioxol-5- ylmethyl)amiono]-6-chloro-2-quinozolinyl]-4-piperidine-carboxylic acid, monosodium salt; (+)-cis-5,6a,7,9,9,9a-hexahydro-2-[4-(trifluoromethyl)-phenylmethyl-5-methyl-cyclopent-4,5]imidazo[2,1-b]purin-4(3H)one; furazlocillin; cis-2-hexyl-5-methyl-3,4,5,6a,7,8,9,9a- octahydrocyclopent[4,5]-imidazo[2,1-b]purin-4-one; 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6- carboxylate; 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylate; 4-bromo-5-(3-pyridylmethylamino)-6-(3-(4-chlorophenyl) propoxy)-3- (2H)pyridazinone; I-methyl-5(5-morpholinoacetyl-2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro- 7H-pyrazolo(4,3-d)pyrimidin-7-one; 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2- quinazolinyl]-4-piperidinecarboxylic acid, monosodium salt; Pharmaprojects No. 4516 (Glaxo Wellcome); Pharmaprojects No. 5051 (Bayer); Pharmaprojects No. 5064 (Kyowa Hakko; see WO 96/26940); Pharmaprojects No. 5069 (Schering Plough); GF-196960 (Glaxo Wellcome); E-8010 and E-4010 (Eisai); Bay-38-3045 & 38-9456 (Bayer) and Sch-51866.

The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

Accordingly the present invention provides for a composition comprising a compound of formula (I), (Ia) or (Ib) and a pharmaceutically acceptable diluent or carrier.

For example, the compounds of the formula (I), (Ia) or (Ib) can be administered orally, buccally or sublingually in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications.

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the formula (I), (Ia) or (Ib) may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents

such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

The compounds of the formula (I), (Ia) or (Ib) can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

The compounds of formula (I), (Ia) or (Ib) can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomiser or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the formula (I), (Ia) or (Ib) and a suitable powder base such as lactose or starch.

Alternatively, the compounds of the formula (I), (Ia) or (Ib) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The compounds of the formula (I), (Ia) or (Ib) may also be dermally or transdermally administered, for example, by the use of a skin patch. They may also be administered by the pulmonary or rectal routes.

They may also be administered by the ocular route. For ophthalmic use, the compounds can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

For application topically to the skin, the compounds of the formula (I), (Ia) or (Ib) can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds of the formula (I), (Ia) or (Ib) may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-

cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

The present invention is further exemplified by the following, non-limiting examples:

The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions are used:

α_D	optical rotation at 587nm.
Arbacel®	filter agent
b	broad
Boc	*tert*-butoxycarbonyl
$CDCl_3$	chloroform-d1
CD_3OD	methanol-d4
δ	chemical shift
d	doublet
dd	double doublet
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
h	hours
HCl	hydrogen chloride
LRMS	low resolution mass spectrum
m	multiplet
m/z	mass spectrum peak
min	minutes
Mpt	melting point
NaOH	sodium hydroxide
NMR	nuclear magnetic resonance
q	quartet

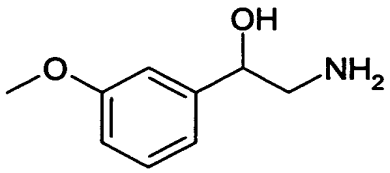
s	singlet
t	triplet
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

Melting points were determined using a Perkin Elmer DSC7 at a heating rate of 20°C/minute).

X-RAY DIFFRACTION DATA WERE RECORDED AT ROOM TEMPERATURE USING A BRUKER AXS SMART-APEX CCD AREA-DETECTOR DIFFRACTOMETER (MO Kα RADIATION). INTENSITIES WERE INTEGRATED FROM SEVERAL SERIES OF EXPOSURES. EACH EXPOSURE COVERED 0.3° IN ω, WITH AN EXPOSURE TIME OF 60 S AND THE TOTAL DATA SET WAS MORE THAN A SPHERE.

Example 1

2-Amino-1-(3-methoxyphenyl)ethanol

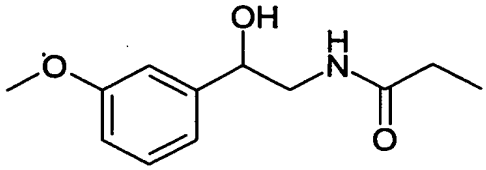


3-Methoxybenzaldehyde (27.2g, 0.2mol) in THF (150ml) was added to a stirred solution of 3N HCl (aq) (150ml, 0.3mol) and sodium sulphite (37.8g, 0.3mol) at room temperature. After 10 minutes potassium cyanide (19.53g, 0.3mol) was added, portion wise, and the reaction mixture was then stirred for 30 minutes. Diethyl ether (800ml) and water (300ml) were added and subsequent layers partitioned. Aqueous re-extracted with diethyl ether (500ml) the organics combined, dried over anhydrous magnesium sulphate, filtered then concentrated *in vacuo* to give the cyanohydrin intermediate as a colourless oil, (35.57g, 0.22mol, >100 %). Borane-tetrahydrofuran complex (1M in THF) (400ml, 0.4mol) was then cautiously added to the cyanohydrin in THF (100ml).

Once effervescence had ceased, stirring was continued at reflux for 1.5 hours under an atmosphere of nitrogen. The reaction mixture was cooled then quenched with methanol (40ml) before concentrating *in vacuo* to give a colourless oil. 6M HCl (aq) (200ml) was added and reaction stirred at reflux for two hours before concentrating *in vacuo* to give a white solid. This was pre-absorbed onto silica then purified by column chromatography eluting with dichloromethane: methanol: ammonia (90:10:1) to give the title compound as a colourless oil (31.3g, 0.19mol, 94%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.60 (bs, 2H), 2.80 (dd, 1H), 3.02 (dd, 1H), 3.46 (s, 1H), 3.81 (s, 3H), 4.60 (dd, 1H), 6.81 (d, 1H), 6.91 (d, 1H), 6.93 (s, 1H), 7.22 (t, 1H). LRMS: m/z 168 ($M-H^+$). Analysis found C, 56.66; H, 8.28; N, 6.91%. $C_9H_{13}NO_2 \cdot 1.33H_2O$ requires C, 56.33; H, 8.27; N, 7.30%.

EXAMPLE 2

N-[2-Hydroxy-2-(3-methoxyphenyl)ethyl]propionamide

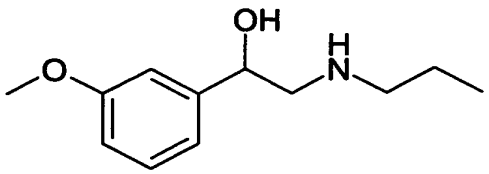


Triethylamine (52ml, 0.37mol) was added to the amine from example 1 (31.3g, 0.19mol) in dichloromethane (400ml) and reaction mixture stirred under an atmosphere of nitrogen gas at 0°C for 10 minutes. Propionyl chloride (16.3ml, 0.19mol) was added and after stirring for 30 minutes, the reaction temperature was raised to room temperature for a further 5 hours. The reaction mixture was quenched 1N HCl (aq) (100ml) and then extracted with dichloromethane (2 x 50ml). The organic fractions were combined, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound as a colourless oil that crystallised on standing to white crystals (28g, 0.13mol, 67%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.18 (t, 3H), 2.22 (q, 2H), 2.51 (bs, 1H), 3.31 (m, 1H), 3.71 (dd, 1H), 3.80 (s, 3H), 4.81 (m, 1H), 5.95 (bs, 1H), 6.80 (d, 1H), 6.90 (d, 1H), 6.91 (s, 1H), 7.22 (t, 1H). LRMS: m/z 224. Mpt: 77-78°C. Analysis

found C, 63.86; H, 7.82; N, 6.28%. $C_{12}H_{17}NO_3 \cdot 0.1H_2O$ requires C, 64.04; H, 7.70; N, 6.22%.

EXAMPLE 3

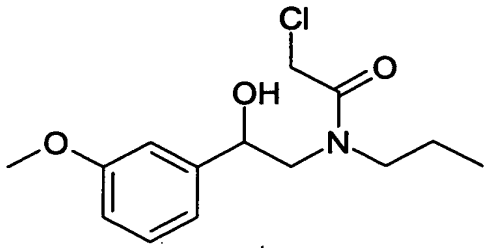
1-(3-Methoxyphenyl)-2-propylaminoethanol



Borane-tetrahydrofuran complex (1M in THF) (376ml, 0.4mol) was added to amide from example 2 (28g, 0.13mol) in dry THF (100ml) then the reaction mixture, stirred under an atmosphere of nitrogen gas, was brought to reflux for 2.5 hours. The reaction mixture was cooled then quenched with methanol (40ml), before concentrating *in vacuo* to give an opaque white oil. 6N HCl (aq) (200ml) was added and reaction stirred at reflux for two hours. The reaction mixture was cooled then dichloromethane (200ml) added and the layers separated. The aqueous layer was rendered basic by addition of potassium carbonate then re-extracted with dichloromethane (2 x 200ml). Organic extracts were combined, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound as a colourless oil that crystallised on standing to give colourless crystals (15.3g, 0.07mol, 59%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 0.93 (t, 3H), 1.62 (q, 2H), 2.71 (q, 2H), 2.81 (t, 2H), 3.00 (d, 1H), 3.80 (s, 3H), 4.30 (bs, 1H), 4.89 (d, 1H), 6.81 (d, 1H), 6.91 (d, 1H), 6.93 (s, 1H), 7.22 (t, 1H). LRMS: m/z 210. Mpt: 50-51°C. Analysis found C, 67.47; H, 9.02; N, 6.45%. $C_{12}H_{19}NO_2 \cdot 0.2H_2O$ requires C, 67.70; H, 9.19; N, 6.58%.

EXAMPLE 4

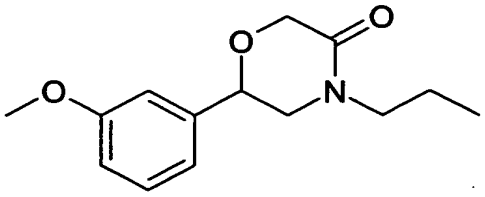
2-Chloro-N-[2-hydroxy-2-(3-methoxyphenyl)ethyl]-N-propylacetamide



Sodium hydroxide (15.1g, 0.38mol) in water (180ml) was added to the amine from example 3 (15.8g, 0.08mol) in dichloromethane (500ml) and the solution vigorously stirred at room temperature. Chloroacetylchloride (7.22ml, 0.09mol) was then added and the reaction mixture stirred for a further 30 minutes. The layers were separated and the aqueous layer re-extracted with dichloromethane (200ml). The organic extracts were combined, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound as a colourless oil (17.8g, 0.06mol, 83%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 0.96 (t, 3H), 1.62 (q, 2H), 3.21 (q, 2H), 3.57-3.71 (m, 2H), 3.82 (s, 3H), 4.01-4.21 (bq, 1H), 4.16 (s, 2H), 5.00 (m, 1H), 6.82 (m, 1H), 6.91-6.99 (m, 2H), 7.22 (m, 1H). LRMS: m/z 286. Analysis found C, 57.38; H, 6.95; N, 4.67%. $C_{14}H_{20}NO_3Cl \cdot 0.33H_2O$ requires C, 57.64; H, 7.14; N, 4.80%.

EXAMPLE 5

6-(3-Methoxyphenyl)-4-propylmorpholin-3-one

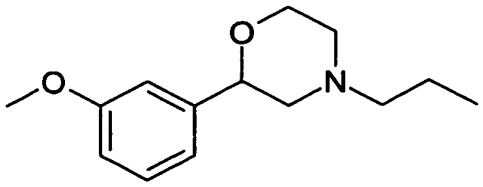


Potassium hydroxide (4.2g, 0.07mol), isopropyl alcohol (500ml) and the amide from example 4 (17.8g, 0.06mol) were stirred together as an opaque solution with water (15ml) for 2 hours. The reaction mixture was concentrated *in vacuo* and the yellow residue dissolved in ethyl acetate (200ml). This was partitioned with water (200ml) then brine (200ml). The organic fraction was dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound as a yellow oil (15.8g, 0.06mol, 100 /). ^{1}H NMR ($CDCl_3$,

400MHz) δ: 0.96 (t, 3H), 1.62 (m, 2H), 3.36 (m, 2H), 3.51 (q, 2H), 3.81 (s, 3H), 4.30-4.62 (bq, 2H), 4.79 (d, 1H), 6.85 (d, 1H), 6.91 (d, 1H), 6.95 (s, 1H), 7.29 (t,1H). LRMS: m/z 272. Analysis found C, 66.80; H, 7.78; N, 5.52%. $C_{14}H_{19}NO_3 \cdot 0.1H_2O$ requires C, 66.96; H, 7.71; N, 5.58%.

EXAMPLE 6

2-(3-Methoxyphenyl)-4-propylmorpholine



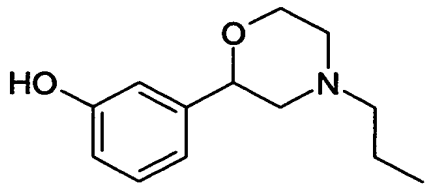
Borane-tetrahydrofuran complex (1M in THF) (200ml, 0.19mol) was added dropwise to the morpholin-3-one from example 5 (15.8g, 0.06mol) in dry THF (100ml) under an atmosphere of nitrogen, over 30 minutes. The reaction mixture was brought to reflux for 3 hours then cooled and quenched by addition of methanol (30ml). The reaction mixture was then concentrated *in vacuo* and the colourless residue cautiously suspended in 4N HCl (aq) (400ml) before refluxing for 2.5 hours. The reaction mixture was cooled and dichloromethane (200ml) added. Layers were separated and the aqueous layer rendered basic by addition of potassium carbonate before re-extracting with dichloromethane (3 x 100ml). The organic extracts were combined, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound as a colourless oil (12.51g, 0.05mol, 84%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 0.95 (t, 3H), 1.59 (q, 2H), 2.05 (t, 1H), 2.23 (t, 1H), 2.40 (t, 2H), 2.81 (d, 1H), 2.98 (d, 1H), 3.80 (s, 3H), 3.85 (t, 1H), 4.05 (d, 1H), 4.60 (d, 1H), 6.81 (d, 1H), 6.91 (d, 1H), 7.21 (t, 1H), 7.23 (s, 1H). LRMS: m/z 236. Analysis found C, 68.94; H, 8.80; N, 5.79%. $C_{14}H_{21}NO_2 \cdot 0.5H_2O$ requires C, 68.82; H, 9.08; N, 5.73%.

EXAMPLE 7A

R-(-)-3-(4-Propylmorpholin-2-yl)phenol

Example 7b

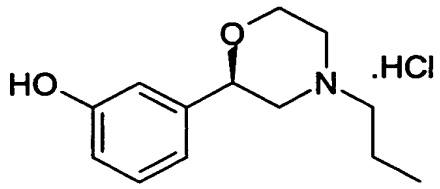
S-(+)-3-(4-Propylmorpholin-2-yl)phenol



Hydrobromic acid (250ml) and the anisole from example 6 (8.62g, 0.03mol) were heated to reflux together for 1 hour. After cooling the reaction mixture was diluted with water (100ml) then neutralised by addition of NH_4OH (20ml). The yellow opaque solution was then extracted with dichloromethane (2 x 100ml). The organic extracts were combined then dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the racemic mixture of the title compound as a yellow oil (7.78g, 0.03mol, 96%). The enantiomers were separated by chiral chromatography (Chiralpak AD 250 * 20mm column) eluting with hexane: isopropyl alcohol: diethylamine (70: 30: 0.05) to give enantiomer 1 (ee > 99.5%) and enantiomer 2 (ee> 99%). Each enantiomer was purified by column chromatography on silica eluting with dichloromethane: methanol (95:5) to give enantiomer 1(7a) (3.02g, 0.014mol, 39%) and enantiomer 2 (7b) (3.15g, 0.014mol, 40%) as colourless oils. Enantiomer 1 (7a): ^1H NMR ($CDCl_3$, 400MHz) δ: 0.96 (t, 3H), 1.60 (q, 2H), 2.13 (t, 1H), 2.31 (t, 1H), 2.41 (t, 2H), 2.85 (d, 1H), 3.02 (d, 1H), 3.90 (t, 1H), 4.02 (dd, 1H), 4.60 (d, 1H), 6.78 (d, 1H), 6.80 (s, 1H), 6.91 (d, 1H), 7.20 (t, 1H). LRMS: m/z 222 ($M-H^+$). Enantiomer 2 (7b): ^1H NMR ($CDCl_3$, 400MHz) δ: 0.96 (t, 3H), 1.60 (q, 2H), 2.13 (t, 1H), 2.31 (t, 1H), 2.41 (t, 2H), 2.85 (d, 1H), 3.02 (d, 1H), 3.90 (t, 1H), 4.02 (dd, 1H), 4.60 (d, 1H), 6.78 (d, 1H), 6.80 (s, 1H), 6.91 (d, 1H), 7.20 (t, 1H). LRMS: m/z 222 ($M-H^+$).

EXAMPLE 8

R-(-)-3-(4-Propylmorpholin-2-yl)phenol hydrochloride



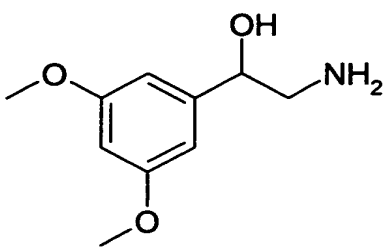
Enantiomer 1 (7a) of example 7 (3.00g, 0.014mol) was dissolved in diethyl ether (180ml) and hydrogen chloride (2.0M solution in diethyl ether) (10ml) was added. The reaction mixture was stirred at room temperature for 30 minutes, then the solvent was decanted and dried *in vacuo,* giving title compound as a white solid (3.115g, 0.012mol, 90%). ^{1}H NMR (CD_3OD, 400MHz) δ: 1.06 (t, 3H), 1.81 (m, 2H), 3.02 (t, 1H), 3.16 (t, 2H), 3.20 (t, 1H), 3.60 (t, 2H), 4.01 (t, 1H), 4.26 (d, 1H), 4.71 (d, 1H), 6.78 (d, 1H), 6.82 (s, 1H), 6.83 (d, 1H), 7.21 (t, 1H). LRMS: m/z 222 ($M-H^+$). Analysis found C, 59.74; H, 7.98; N, 5.25%. $C_{13}H_{19}NO_2 \cdot 0.18H_2O$ requires C, 59.82; H, 7.86; N, 5.37%. α_D = -5.66° (Methanol 10.6mg/ 10ml).

A SAMPLE OF THE TITLE COMPOUND WAS RE CRYSTALLISED BY VAPOUR DIFFUSION USING A METHANOL: DIETHYL ETHER MIX AND AN X-RAY CRYSTAL STRUCTURE OBTAINED. THE ABSOLUTE STEREOCHEMISTRY OF THE TITLE COMPOUND WAS DETERMINED FROM THE DIFFRACTION DATA BY THE METHOD OF FLACK[1] AND WAS SHOWN TO HAVE AN 'R' CONFIGURATION.

REF 1: H.D.FLACK, *ACTA CRYST.* 1983, 439, 876-881

EXAMPLE 9

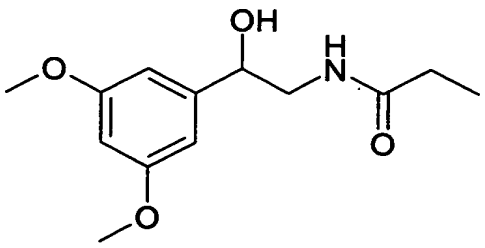
2-Amino-1-(3,5-dimethoxyphenyl)ethanol



Prepared following the same method as for example 1 starting from 3,5-dimethoxybenzaldehyde (5.00g, 0.03mol). After refluxing in 6M HCl (aq) the reaction mixture was cooled and extracted with diethyl ether (2 x 80ml). The organic layers were discarded and the aqueous layer basified by the addition of potassium carbonate. The aqueous residue was then extracted with ethyl acetate (3 x 70ml). The organic extracts were combined and dried over anhydrous magnesium sulphate, filtered and concentrated in vacuo to give the title compound as a pale yellow oil (3.47g, 0.018mol, 59%). ^{1}H NMR (CD_3OD, 400MHz) δ: 2.77 – 2.86 (m, 2H), 3.78 (s, 6H), 4.60 (m, 1H), 6.38 (s, 1H), 6.52 (s, 2H). LRMS: m/z 198 ($M-H^+$).

EXAMPLE 10

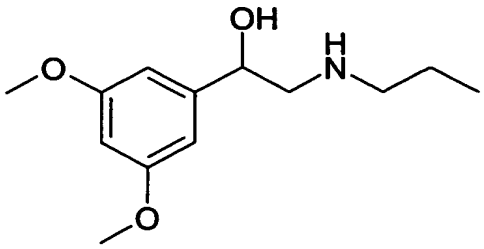
N-[2-(3,5-dimethoxyphenyl)-2-hydroxyethyl]propionamide



Prepared following the same method as for example 2 starting from the amine in example 9 (3.41g, 0.017mol). The crude reaction mixture was purified by column chromatography on silica eluting with dichloromethane: methanol (95:5) to give the title compound as a bright yellow oil (3.08g, 0.012mol, 70%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.18 (m, 3H), 2.24 (m, 2H), 3.34 (m, 1H), 3.68 (m, 1H), 3.81 (s, 6H), 4.80 (dd, 1H), 5.95 (bs, 1H), 6.39 (s, 1H), 6.51 (s, 2H). LRMS: m/z 252 ($M-H^-$).

EXAMPLE 11

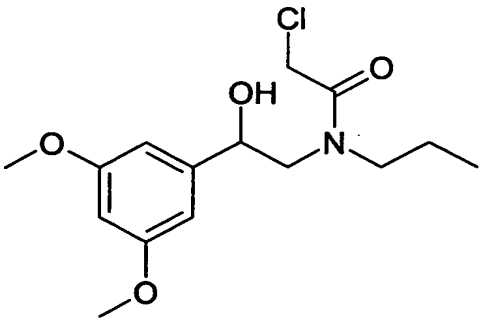
1-(3,5-dimethoxyphenyl)-2-propylaminoethanol



Prepared following the method as for example 3 starting from the amide in example 10 (3.06g, 0.012mol) to give the title compound as an orange oil (2.72g, 0.011mol, 94%). ^{1}H NMR (CD_3OD, 400MHz) δ: 0.95 (t, 3H), 1.56 (m, 2H), 2.61 (m, 2H), 2.77 (d, 2H), 3.78 (s, 6H), 4.70 (t, 1H), 6.38 (s, 1H), 6.51 (s, 2H). LRMS: m/z 240 ($M-H^+$).

EXAMPLE 12

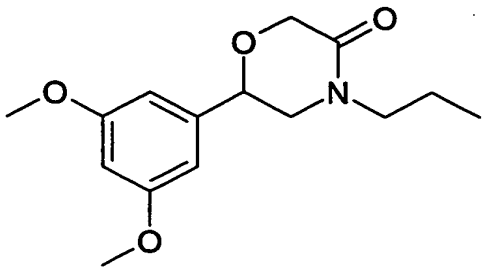
2-Chloro-N-[2--(3,5-dimethoxyphenyl)-2-hydroxyethyl]-N-propylacetamide



Prepared following the same method as for example 4 starting from the amine in example 11 (2.70g, 0.011mol) to give the title compound as a yellow oil (3.56g, 0.011mol, 100%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 0.92 (t, 3H), 1.61 (m, 2H), 3.20 (m, 2H), 3.51 –3.64 (m, 2H), 3.80 (d, 6H), 4.13 (s, 2H), 4.95 (m, 1H), 6.40 (m, 1H), 6.55 (s, 2H). LRMS: m/z 316 ($M-H^+$).

EXAMPLE 13

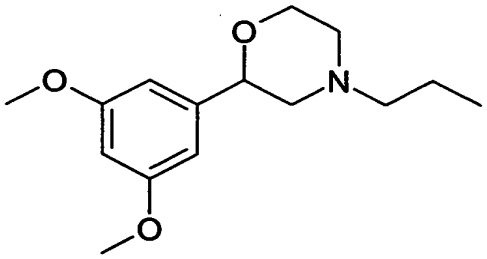
6-(3,5-Dimethoxyphenyl)-4-propylmorpholin-3-one



Prepared following the same method as for example 5 starting from the amide in example 12 (3.54g, 0.011mol) to give the title compound as a yellow oil (2.44g, 0.009mol, 78%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 0.94 (t, 3H), 1.61 (m, 2H), 3.30 (m, 2H), 3.49 (m, 2H), 3.80 (s, 6H), 4.30 (d, 1H), 4.42 (d, 1H), 4.73 (dd, 1H), 6.42 (s, 1H), 6.53 (s, 2H). LRMS: m/z 280 ($M-H^+$).

EXAMPLE 14

2-(3,5-Dimethoxyphenyl)-4-propylmorpholine



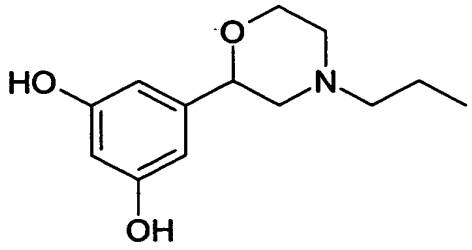
Prepared following the method as for example 6 starting from the amide in example 13 (2.42g, 0.009mol). After refluxing in 6M HCl (aq) the cooled reaction mixture was extracted with diethyl ether (2 x 80ml). The organic layers were discarded and the aqueous basified by addition of potassium carbonate. The aqueous residue was then extracted with ethyl acetate (3 x 80ml) and the organic extracts combined, dried over anhydrous magnesium sulphate, filtered then concentrated *in vacuo* to give the title compound as a pale orange oil (2.14g, 0.008mol, 93%). ^{1}H NMR (CD_3OD, 400MHz) δ: 0.95 (t, 3H), 1.58 (m, 2H), 2.01 (m, 1H), 2.22 (dt, 1H), 2.38 (t, 2H), 2.83 (d, 1H), 2.93 (d, 1H), 3.78 (m, 7H), 4.01 (dd, 1H), 4.45 (dd, 1H), 6.39 (s, 1H), 6.49 (s, 2H). LRMS: m/z 266 ($M-H^+$).

EXAMPLE 15A

R-5-(4-Propylmorpholin-2-yl)benzene-1, 3-diol

Example 15b

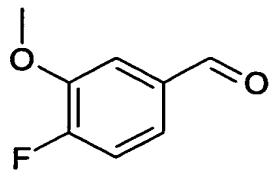
S-5-(4-Propylmorpholin-2-yl)benzene-1, 3-diol



Prepared following the same route as for example 7 starting from the 3,5-dimethoxyphenyl compound in example 14 (1.00g, 0.004mol) giving the title racemic compound as a brown oil (145mg, 0.61mmol,16%). The enantiomers were separated by chiral chromatography (Chiralpak AD 250 * 20mm column) eluting with hexane: isopropyl alcohol: (80: 20) to give enantiomer 1 (15a) (5.2mg) (ee > 98.94%) and enantiomer 2 (15b) (5.1mg) (ee > 96.46%) as brown oils. Enantiomer 1 (15a): ^{1}H NMR (CD_3OD, 400MHz) δ: 0.96 (t, 3H), 1.58 (m, 2H), 2.01 (t, 1H), 2.20 (dt, 1H), 2.37 (t, 2H), 2.81 - 2.92 (m, 2H), 3.89 (dt, 1H), 3.99 (dd, 1H), 4.38 (dd, 1H), 6.18 (t, 1H), 6.26 (s, 2H). LRMS: m/z 238 (M-H^+). Enantiomer 2 (15b): ^{1}H NMR (CD_3OD, 400MHz) δ: 0.95 (t, 3H), 1.58 (m, 2H), 2.01 (t, 1H), 2.20 (dt, 1H), 2.38 (t, 2H), 2.80 - 2.92 (q, 2H), 3.78 (dt, 1H), 3.98 (dd, 1H), 4.38 (dd, 1H), 6.18 (s, 1H), 6.25 (s, 2H). LRMS: m/z 238 (M-H^+).

EXAMPLE 16

4-Fluoro-3-methoxybenzaldehyde

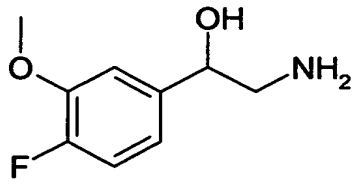


(4-Fluoro-3-methoxyphenyl) methanol (5.00g, 0.03mol) and manganese dioxide (33.4g, 0.38mol) were stirred in dichloromethane (100ml) under an atmosphere of nitrogen, at gentle reflux for 16 hours. The cooled reaction mixture was then

filtered through arbacel and concentrated *in vacuo* to give the title compound as a white solid (4.18g, 0.027mol, 85%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 3.96 (s, 3H), 7.23 (d, 1H), 7.43 (m, 1H), 7.50 (d, 1H) 9.91 (s, 1H). Mpt: 61-63°C. Analysis found C, 62.18; H, 4.54%. $C_8H_7FO_2$ requires C, 62.34; H, 4.58%.

EXAMPLE 17

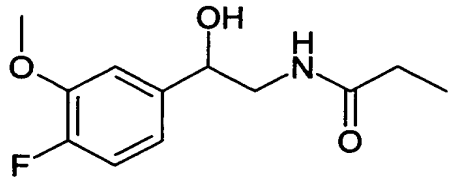
2-Amino-1-(4-fluoro-3-methoxyphenyl)ethanol



Prepared following the same method as for example 1 starting from 4-fluoro-3-methoxybenzaldehyde (4.17g, 0.03mol). After refluxing in 6M HCl (aq) the reaction mixture was cooled and extracted with diethyl ether (2 x 60ml). The organic layers were discarded and the aqueous layer basified by the addition of potassium carbonate. The aqueous residue was then extracted with ethyl acetate (3 x 80ml). The organic extracts were combined and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound as an orange oil (2.36g, 0.013mol, 47%). ^{1}H NMR (CD_3OD, 400MHz) δ: 2.80 –2.91 (m, 2H), 3.86 (s, 3H), 4.64 (m, 1H), 6.89 (m, 1H), 7.03 (t, 1H), 7.11 (dd, 1H). LRMS: m/z 186 ($M-H^+$).

EXAMPLE 18

N-[2-(4-Fluoro-3-methoxyphenyl)-2-hydroxyethyl]propionamide

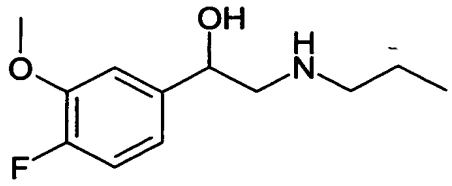


Prepared following the same method as for example 2 starting with the amine from example 17 (1.32g, 0.007mol). The crude reaction mixture was purified by column chromatography on silica eluting with ethyl acetate: pentane (2:1) to

give the title compound as a yellow oil that crystallised on standing (0.59g, 0.002mol, 35%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.18 (t, 3H), 2.24 (q, 2H), 2.58 (bs, 1H), 3.34 (m, 1H), 3.63 (m, 1H), 3.88 (s, 3H), 4.82 (dd, 1H), 5.98 (bs, 1H), 6.82 (m, 1H), 7.01 (m, 2H). LRMS: m/z 242 ($M-H^+$).

EXAMPLE 19

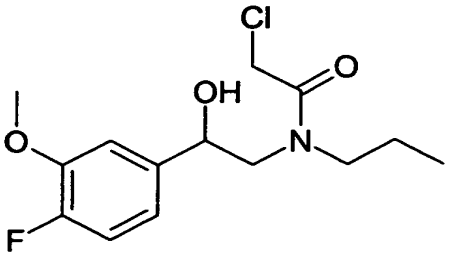
1-(4-Fluoro-3-methoxyphenyl)-2-propylaminoethanol



Prepared following the same method as for example 3 starting with the amide from example 18 (585mg, 2.42mmol). After refluxing in 6M HCl (aq) the reaction mixture was cooled and extracted with diethyl ether (2 x 50ml). The organic layers were discarded and the aqueous layer basified by the addition of potassium carbonate. The aqueous residue was then extracted with ethyl acetate (3 x 50ml). The organic extracts were combined and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound as a pale yellow oil (448mg, 1.97mmol, 81%). ^{1}H NMR (CD_3OD, 400MHz) δ: 0.96 (t, 3H), 1.58 (m, 2H), 2.63 (m, 2H), 2.79 (d, 2H), 3.96 (s, 3H), 4.77 (t, 1H), 6.90 (m, 1H), 7.03 (t, 1H), 7.11 (d, 1H). LRMS: m/z 228 ($M-H^+$).

EXAMPLE 20

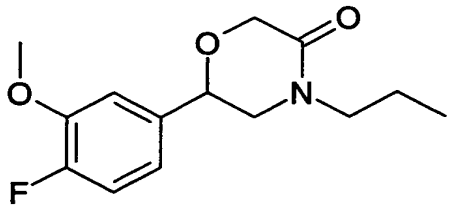
2-Chloro-N-[2-(4-fluoro-3-methoxyphenyl)-2-hydroxyethyl]-N-propylacetamide



Prepared following the same method as for example 4 starting with the amine from example 19 (0.84g, 4.00mmol) to give the title compound as a yellow oil (0.97g, 3.00mmol, 87%). LRMS: m/z 304 ($M-H^+$). This was taken on crude.

EXAMPLE 21

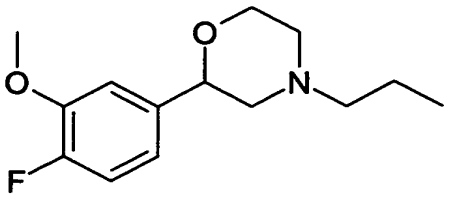
6-(4-Fluoro-3-methoxyphenyl)-4-propylmorpholin-3-one



Prepared following the same method as for example 5 starting with the amide from example 20 (0.96g, 3.00mmol) to give the title compound as a yellow oil (0.64g, 2.40mmol, 75%). ^1H NMR ($CDCl_3$, 400MHz) δ: 0.94 (t, 3H), 1.62 (m, 2H), 3.33 (m, 2H), 3.48 (m, 2H), 3.91 (s, 3H), 4.34 (d, 1H), 4.43 (d, 1H), 4.76 (dd, 1H), 6.85 (m, 1H), 7.01 - 7.08 (m, 2H). LRMS: m/z 268 ($M-H^+$).

EXAMPLE 22

2-(4-Fluoro-3-methoxyphenyl)-4-propylmorpholine



Prepared following the same method as for example 6 starting with the morpholin-3-one from example 21 (633mg, 2.37mmol). After refluxing in 6M HCl (aq) the reaction mixture was cooled and extracted with diethyl ether (2 x 20ml). The organic layers were discarded and the aqueous layer basified by the addition of potassium carbonate. The aqueous residue was then extracted with ethyl acetate (3 x 20ml). The organic extracts were combined and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound as a yellow oil (552mg, 2.18mmol, 92 %). ^1H NMR (CD_3OD,

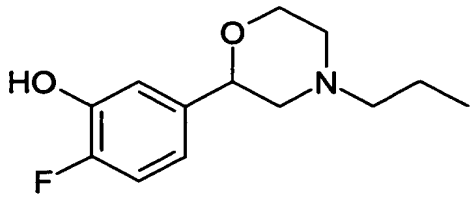
400MHz) δ: 0.95 (t, 3H), 1.58 (m, 2H), 2.02 (t, 1H), 2.22 (dt, 1H), 2.38 (t, 2H), 2.85 (d, 1H), 2.93 (d, 1H), 3.80 (m, 1H), 3.84 (s, 3H), 4.01 (dd, 1H), 4.50 (dd, 1H), 6.88 (m, 1H), 7.02 (t, 1H), 7.09 (d, 1H). LRMS: m/z 254 ($M-H^+$).

EXAMPLE 23A

R-(+)-2-Fluoro-5-(4-propylmorpholin-2-yl)phenol

Example 23b

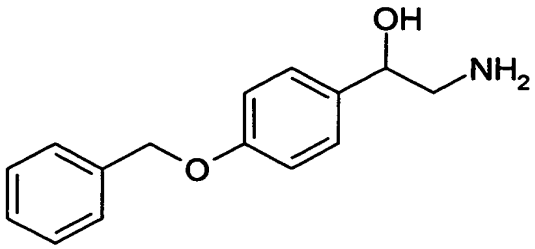
S-(-)-2-Fluoro-5-(4-propylmorpholin-2-yl)phenol



Prepared following the same method as for example 7 starting with the anisole from example 22 (200mg, 0.789mmol). The crude reaction mixture was purified by column chromatography on silica eluting with dichloromethane: methanol (90:10) to give the title racemic compound as a dark yellow viscous oil (149mg, 0.62mmol, 79%). The enantiomers were separated by chiral chromatography (Chiralpak AD 250 * 20mm column) eluting with hexane: isopropyl alcohol: (90: 10) to give enantiomer 1 (23a) as an opaque oil (15mg) (ee > 99.5%) and enantiomer 2 (23b) as a crystalline solid (16mg) (ee> 99%). Enantiomer 1 (23a): ^1H NMR (CD_3OD, 400MHz) δ: 0.95 (t, 3H), 1.58 (m, 2H), 2.01 (t, 1H), 2.21 (dt, 1H), 2.37 (t, 2H), 2.82 - 2.97 (bq, 2H), 3.78 (dt, 1H), 3.99 (dd, 1H), 4.43 (d, 1H), 6.78 (m, 1H), 6.89 -7.01 (m, 2H). LRMS: m/z 240 ($M-H^+$). α_D = +0.91 (Ethanol 1.10mg/ ml). Enantiomer 2 (23b): ^1H NMR (CD_3OD, 400MHz) δ: 0.96 (t, 3H), 1.58 (m, 2H), 2.01 (t, 1H), 2.22 (dt, 1H), 2.38 (t, 2H), 2.78 (dd, 2H), 3.78 (dt, 1H), 4.00 (dd, 1H), 4.43 (dd, 1H), 6.78 (m, 1H), 6.91 (d, 1H), 6.98 (t, 1H). LRMS: m/z 240 ($M-H^+$). α_D = -0.40 (Ethanol 1.00mg/ ml).

EXAMPLE 24

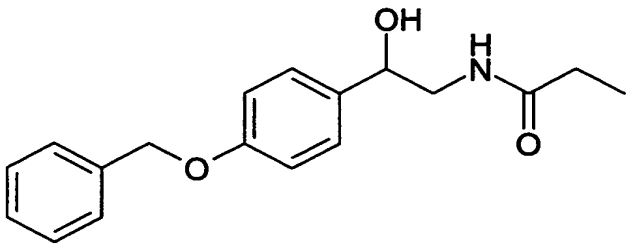
2-Amino-1-(4-benzyloxyphenyl)ethanol



Potassium cyanide (20.15g, 0.31mol) and ammonium chloride (16.4g, 0.31mol) were dissolved in water (60ml) to which was added 4-benzyloxybenzaldehyde (32.9g, 0.155mol) followed by diethyl ether (100ml). The reaction mixture was stirred vigorously for 48 hours at room temperature before extracting with ethyl acetate (2 x 200ml). The combined organic layers were dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the cyanohydrin intermediate as a yellow solid (34.2g, 0.14mol, 90%). The cyanohydrin was then dissolved in dry THF (300ml) and borane-methyl sulphide complex (26.6ml, 0.28mol) was added. The reaction mixture was refluxed for 2 hours before being quenched with methanol (50ml). Water (50ml) was added followed by c.HCl (40ml) and the reaction mixture was stirred for 2 hours until the exotherm subsided. The reaction mixture was then concentrated *in vacuo* and the residue diluted with water (100ml). The aqueous solution was then basified by addition of NH_4OH (30ml), and extracted with ethyl acetate (3 x 150ml). The organic extracts were dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound as a white solid (24.8g, 0.10mol, 73%). ^1H NMR ($CDCl_3$, 400MHz) δ: 1.62 (bs, 3H), 2.81 (dd, 1H), 2.99 (d, 1H), 4.61 (q, 1H), 5.07 (s, 2H), 6.95 (d, 2H), 7.22-7.45 (m, 7H). LRMS: m/z 244 ($M-H^+$).

EXAMPLE 25

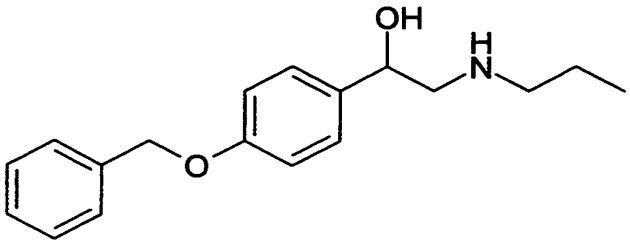
N-[2-(4-BENZYLOXYLPHENYL)-2-HYDROXYETHYL)PROPIONAMIDE



The amine from example 24 (24.8g, 0.10mol) was dissolved in dichloromethane (700ml) and to this was added triethylamine (20.86ml, 0.15mol). The reaction mixture was stirred and cooled to 0°C, before propionyl chloride (7.12ml, 0.082mol) was added dropwise. The reaction mixture was then allowed to warm to room temperature over 16 hours before quenching with 3M HCl (aq) (20ml) and water (100ml). The reaction mixture was then extracted with dichloromethane (3 x 200ml) and the combined organic layers dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound as a clear viscous gum (27.5g, 0.092mol, 90%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.10 (t, 3H), 2.19 (q, 2H), 3.32-3.43 (m, 4H), 4.81 (s, 2H), 5.11 (m, 1H), 6.99 (d, 2H), 7.25- 7.42 (m, 7H). LRMS: m/z 298 ($M-H^-$).

EXAMPLE 26

<u>1-(4-benzyloxyphenyl)-2-propylaminoethanol</u>

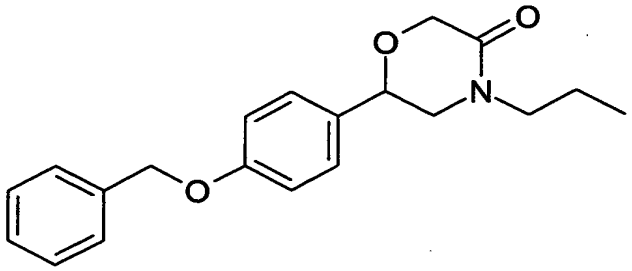


To the amide from example 25 (27.5g, 0.092mol) in dry THF (100ml) was added borane-methyl sulphide complex (17.5ml, 0.18mol) and the reaction mixture was stirred at reflux for 2 hours. The reaction mixture was cooled then quenched with methanol (30ml). Water (50ml) and c.HCl (35ml) were added

and the reaction mixture stirred until all bubbling ceased before concentrating *in vacuo*. To the residue water (250ml) was added, before basifying by addition of NH_4OH (30ml). The aqueous layer was extracted with ethyl acetate (3 x 200ml) and the combined organic extracts dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound as a white solid (26.1g, 0.09mol, 99%). ^1H NMR (CD_3OD, 400MHz) δ: 0.95 (t, 3H), 1.58 (q, 2H), 2.62 (m, 2H), 2.81 (m, 2H), 4.72 (dd, 1H), 5.05 (s, 2H), 6.95 (d, 2H), 7.24 (m, 3H), 7.35 (t, 2H), 7.41 (d, 2H). LRMS: m/z 286 ($M-H^+$).

EXAMPLE 27

6-(4-benzyloxyphenyl)-4-propylmorpholin-3-one

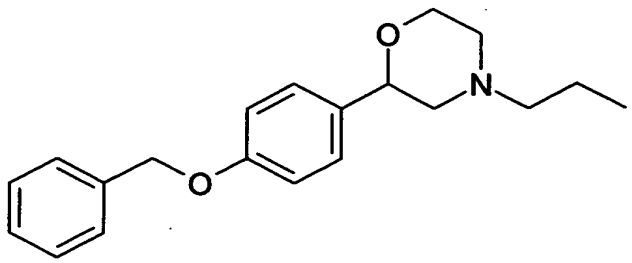


Sodium hydroxide (22.5g, 0.56mol) in water (100ml) was added to the amine from example 26 (26.0g, 0.09mol) in dichloromethane (400ml) and the solution vigorously stirred at room temperature. Chloroacetylchloride (8.6ml, 0.11mol) was then added and the reaction mixture stirred for a further 60 minutes. The layers were separated and the aqueous layer re-extracted with dichloromethane (200ml). The organic extracts were combined, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give a colourless oil. Potassium hydroxide (15.0g, 0.27mol), isopropyl alcohol (400ml) and the colourless oil residue were stirred together as an opaque solution with water (30ml) for 2 hours. The reaction mixture was concentrated *in vacuo* and the yellow residue dissolved in ethyl acetate (200ml). This was partitioned with water (200ml) then brine (200ml). The organic fraction was dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound as a white solid (19.9g, 0.06mol, 67%). ^1H NMR ($CDCl_3$, 400MHz) δ: 0.95 (t, 3H), 1.62 (m, 2H), 3.34 (m, 2H), 3.51 (m, 2H), 4.32 (d, 1H),

4.41 (d, 1H), 4.72 (dd, 1H), 5.04 (s, 2H), 6.98 (d, 2H), 7.31-7.43 (m, 7H). LRMS: m/z 326 ($M-H^+$).

EXAMPLE 28

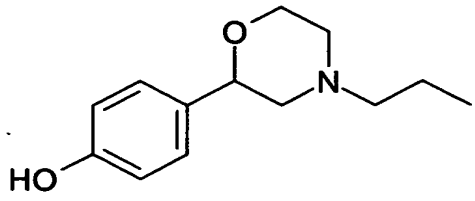
2-(4-benzyloxyphenyl)-4-propylmorpholine



Prepared following the same method as for example 26 with the morpholin-3-one from example 27 (19.9g, 0.061mol) to give the title compound as a colourless oil (17g, 0.055mol, 90%). ^1H NMR ($CDCl_3$, 400MHz) δ: 0.95 (t, 3H), 1.55 (q, 2H), 2.06 (t, 1H), 2.21 (dt, 1H), 2.35 (dd, 2H), 2.80 (d, 1H), 2.91 (d, 1H), 3.82 (dt, 1H), 4.02 (dd, 1H), 4.52 (dd, 1H), 5.05 (s, 2H), 6.98 (t, 2H), 7.24-7.42 (m, 7H). LRMS: m/z 312 ($M-H^+$).

EXAMPLE 29

4-(4-Propylmorpholin-2-yl)phenol

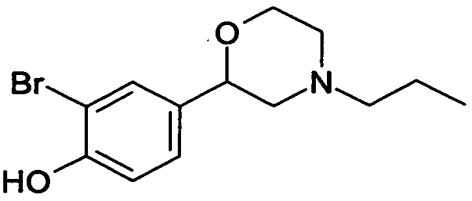


Benzyl ether from example 28 (3.0g, 9.64mmol) was dissolved in methanol (150ml) and 10% palladium on charcoal (800mg) was added. The reaction mixture was stirred for a few minutes before ammonium formate (6.17g, 96.4mmol) was added portionwise. The reaction mixture was carefully heated to 80°C until gas evolution had ceased. After cooling, the reaction mixture was filtered through arbacel, washed with methanol (50ml) and concentrated *in vacuo* to give the title compound as a white crystalline solid (1.51g, 6.83mmol,

71%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 0.91 (t, 3H), 1.58 (q, 2H), 2.10 (t, 1H), 2.22 (t, 1H), 2.40 (dd, 2H), 2.81 (d, 1H), 2.93 (d, 1H), 3.85 (t, 1H), 4.02 (dd, 1H), 4.57 (d, 1H), 6.79 (d, 2H), 7.21 (d, 2H). LRMS: m/z 222 ($M-H^+$).

EXAMPLE 30

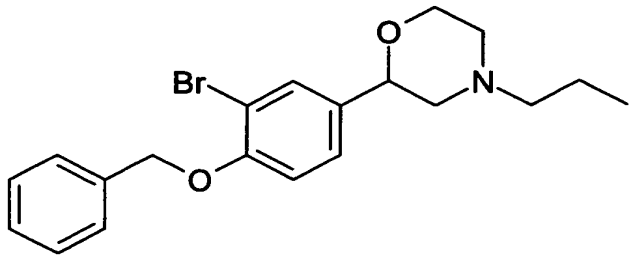
2-Bromo-4-(4-propylmorpholin-2-yl)phenol



To the phenol from example 29 (200mg, 0.9mmol) in dichloromethane (5ml) was added N-bromosuccinimide (161mg, 0.9mmol). The reaction mixture was stirred at room temperature for 55 hours, before concentrating *in vacuo*. The crude product was purified by column chromatography on silica eluting with dichloromethane: methanol (95:5) to give the title compound as a white foam (117.5mg, 0.39mmol, 44%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 0.96 (t, 3H), 1.59 (q, 2H), 2.03 (t, 1H), 2.23 (t, 1H), 2.40 (t, 2H), 2.81 (d, 1H), 2.98 (d, 1H), 3.82 (t, 1H), 4.01 (d, 1H), 4.56 (d, 1H), 6.96 (d, 1H), 7.20 (d, 1H), 7.49 (s, 1H). LRMS: m/z 302 ($M-H^+$, Br isotope).

EXAMPLE 31

2-(4-benzyloxy-3-bromophenyl)-4-propylmorpholine

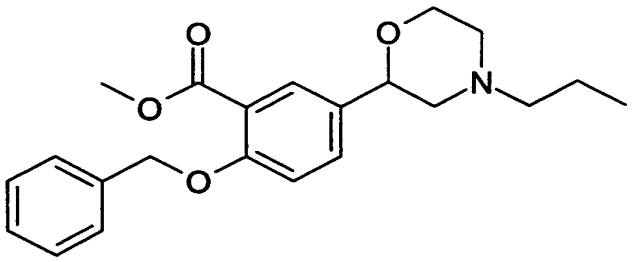


To the phenol from example 30 (117.5mg, 0.39mmol) in dry DMF (10ml), under an atmosphere of nitrogen, was added potassium carbonate (75mg, 0.54mmol) and benzyl bromide (0.07ml, 0.54mmol). The reaction mixture was heated to

150°C for 48 hours. After cooling, the reaction mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate (50ml) and water (50ml). The aqueous layer was then re-extracted with ethyl acetate (2 x 20ml). The combined organic extracts were then dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the crude product as a brown oil. This was purified by column chromatography on silica eluting with dichloromethane: methanol (98:2) to give the title compound as a colourless oil (153mg, 0.39mmol, 100%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 0.93 (t, 3H), 1.56 (q, 2H), 2.05 (t, 1H), 2.25 (t,1H), 2.37 (t, 2H), 2.82 (d, 1H), 2.92 (d, 1H), 3.85 (t, 1H), 4.02 (d, 1H), 4.52 (d, 1H), 5.15 (s, 2H), 6.87 (d, 1H), 7.20 (d, 1H), 7.30 (d, 1H), 7.37 (t, 2H), 7.45 (d, 2H), 7.58 (s, 1H). LRMS: m/z 392 ($M-H^+$).

EXAMPLE 32

2-Benzyloxy-5-(4-propylmorpholin-2-yl)benzoic acid methyl ester

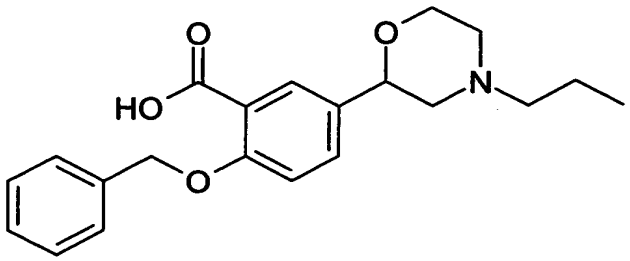


To the bromide from example 31 (153mg, 0.39mmol) in dry DMF (4ml) was added triethylamine (2.1ml, 0.78mmol) and methanol (2ml) and the reaction mixture stirred for 5 minutes. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (1:1) (16mg, 0.02mmol) was added before carbon monoxide (g) (3 inflated balloons) was bubbled through the reaction mixture. The reaction mixture was then heated to 100°C for 16 hours under an atmosphere of carbon monoxide. After cooling, the reaction mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate (25ml) and water (20ml). The organic layer was separated, washed with brine (20ml) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give a black solid. Purification by column chromatography on silica eluting with

dichloromethane: methanol: ammonia (90:10:1) gave the title compound as a colourless oil (105mg, 0.28mmol, 73%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 0.94 (t, 3H), 1.60 (m, 2H), 2.18 (s, 4H), 2.43 (m, 2H), 3.00 (m, 2H), 3.90 (s, 3H), 4.04 d, 1H), 5.18 (s, 2H), 5.97 (d, 1H), 7.26-7.47 (m, 6H), 7.82 (s, 1H). LRMS: m/z 370 ($M-H^+$).

EXAMPLE 33

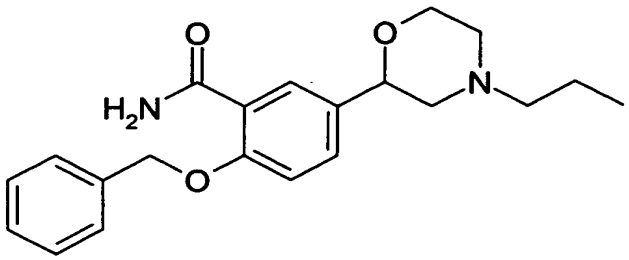
2-Benzyloxy-5-(4-propylmorpholin-2-yl)benzoic acid



To the methyl ester from example 32 (105mg, 0.28mmol) in methanol (5ml) was added 10% sodium hydroxide (aq) (15ml) and the milky white suspension was refluxed for 2 hours. The now colourless reaction mixture was cooled then neutralised by addition of 2M HCl (aq) (few drops). The reaction mixture was then concentrated *in vacuo* to give the title compound as an off-white solid (99mg, 0.28mmol, 100%). LRMS: m/z 355 ($M-H^+$). This material was taken on crude to example 34.

EXAMPLE 34

2-Benzyloxy-5-(4-propylmorpholin-2-yl)benzamide

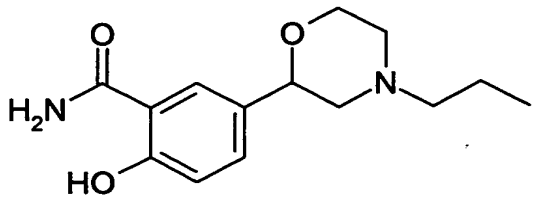


To the crude benzoic acid from example 33 (99mg, 0.28mmol) was added thionyl chloride (5ml) and the reaction mixture heated to 50°C for 2 hours. The

reaction mixture was cooled and the excess thionyl chloride was removed *in vacuo*. The residue was then dissolved in dichloromethane (10ml) and ammonia (g) was bubbled through the reaction mixture for 10 minutes. The resulting suspension was stirred at room temperature for 1 hour before concentrating *in vacuo*. The crude material was purified by column chromatography on silica eluting with dichloromethane: methanol: ammonia (95:5:0.5) to give the title compound as an off-white solid (88mg, 0.25mmol, 90%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 0.94 (t, 3H), 1.59 (m, 2H), 2.15-2.42 (m, 4H), 2.87 (m, 1H), 3.03 (m, 1H), 3.96 (m, 1H), 4.02 (d, 1H), 4.67 (m, 1H), 5.19 (s, 2H), 5.72 (m, 1H), 7.04 (d, 1H), 7.41 (m, 5H), 7.50 (d, 1H), 7.70 (m, 1H), 8.21 (s, 1H). LRMS: m/z 355 ($M-H^+$).

EXAMPLE 35

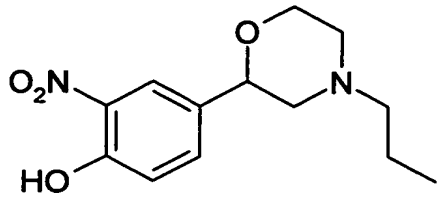
2-Hydroxy-5-(4-propylmorpholin-2-yl)benzamide



Prepared using the same method as for example 29 with the benzyl ester from example 34 (80mg, 0.22mmol) to give the title compound as an off-white solid (56mg, 0.21mmol, 96%). ^{1}H NMR (CD_3OD, 400MHz) δ: 0.95 (t, 3H), 1.55 (m, 2H), 2.13 (t, 1H), 2.29 (t, 1H), 2.42 (m, 2H), 2.88 (d, 1H), 2.97 (d, 1H), 3.81 (t, 1H), 4.00 (d, 1H), 4.49 (d, 1H), 6.87 (d, 1H), 7.42 (d, 1H), 7.78 (s, 1H). LRMS: m/z 265 ($M-H^+$).

EXAMPLE 36

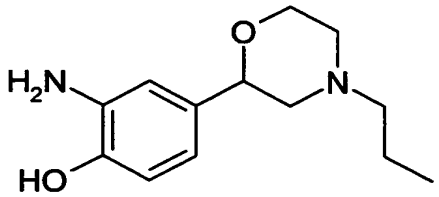
2-Nitro-4-(4-propylmorpholin-2-yl)phenol



The phenol from example 29 (100mg, 0.45mmol) was dissolved in nitric acid: water (1:3) (2ml) and stirred at room temperature for 10 minutes. The reaction mixture was then diluted with water (5ml) and basified with NH_4OH (1ml), before extracting into ethyl acetate (3 x 10ml). The organic extracts were combined and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound as a yellow solid (95mg, 0.35mmol, 79%). ^1H NMR ($CDCl_3$, 400MHz) δ: 0.97 (t, 3H), 1.33 (t, 2H), 1.43-1.79 (bm, 4H), 2.02 (d, 3H), 4.06 (m, 2H), 7.17 (d, 1H), 7.60 (d, 1H), 8.16 (s, 1H), 10.55 (bs, 1H). LRMS: m/z 267 ($M-H^+$).

EXAMPLE 37

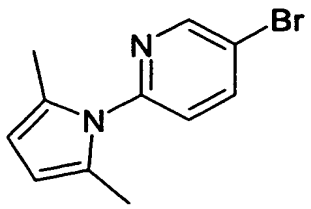
2-Amino-4-(4-propylmorpholin-2-yl)phenol



To the nitro from example 36 (95mg, 0.35mmol) in ethanol (10ml) was added 10% palladium on charcoal (50mg) and ammonium formate (100mg, XS). The reaction mixture was gently heated to 70°C and held at this temperature for 1 hour before it was allowed to cool to room temperature. The reaction mixture was then filtered through arbacel and washed with ethanol (20ml) then dichloromethane (20ml). The organic washes were combined and concentrated *in vacuo* to give the title compound as a yellow solid (65mg, 0.28mmol, 78%). ^1H NMR ($CDCl_3$, 400MHz) δ: 0.91 (t, 3H), 1.55 (m, 2H), 2.12 (t, 1H), 2.25 (dt, 1H), 2.40 (t, 2H), 2.81-2.92 (dd, 2H), 3.82 (t, 1H), 4.00 (d, 1H), 4.42 (d, 1H), 6.60 (m, 2H), 6.71 (s, 1H). LRMS: m/z 237 ($M-H^+$).

EXAMPLE 38

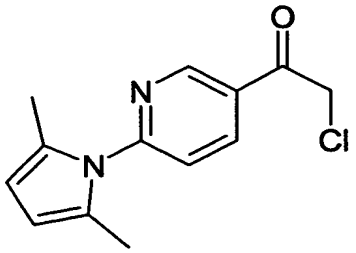
5-Bromo-2-(2,5-dimethylpyrrol-1-yl pyridine



5-Bromopyridin-2-yl-amine (13.8g, 0.08mol), acetonylacetone (14.1ml, 0.12mol) and *p*-toluenesulphonic acid (100mg) were dissolved in toluene (180ml) and refluxed under Dean Stark conditions for 14 hours. After cooling, the brown solution was poured into water (200ml) and extracted with toluene (2 x 200ml). The organic extracts were combined and washed with brine (50ml) then dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give crude product. This was purified by column chromatography on silica eluting with ethyl acetate: pentane (1:3) to give the title compound as a brown oil (18.4g, 0.073mol, 92%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 2.18 (s, 6H), 5.90 (s, 2H), 7.11 (d, 1H), 7.92 (d, 1H), 8.62 (s, 1H). LRMS: m/z 253 ($M-H^+$, Br isotope).

EXAMPLE 39

2-Chloro-1-[6-(2,5-dimethylpyrrol-1-yl)pyridin-3-yl]ethanone

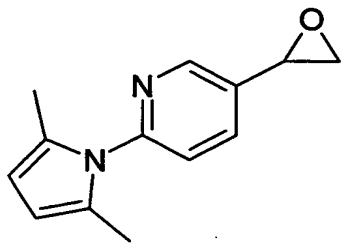


To a solution of bromo pyridine from example 38 (2g, 8.0mmol) at –78°C, in dry THF (30ml), was added butyllithium (2.5M in hexanes) (3.5ml 8.8mmol), dropwise over 20 minutes. The reaction mixture was stirred for 30 minutes then 2-chloro-N-methoxy-N-methylacetamide (1.2g, 8.8mmol) in dry THF (20ml) was added dropwise keeping the temperature at –78°C. Stirring was continued for 30 minutes at this temperature before 1M HCl (aq) (50ml) was added and the

reaction mixture warmed to room temperature. The organic layer was separated and the aqueous layer washed with ethyl acetate (50ml). The organic layers were combined then washed with 3M NaOH (aq) (10ml) and brine (10ml) before being dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give crude title compound as a brown oil (1.34g, 5.4mmol, 67%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 2.20 (s, 6H), 4.68 (s, 2H), 5.92 (s, 2H), 7.32 (d, 1H), 8.38 (d, 1H), 9.16 (s, 1H). LRMS: m/z 249 ($M-H^+$).

EXAMPLE 40

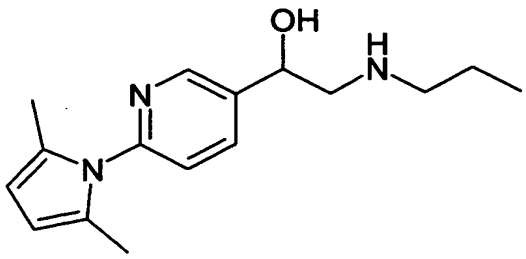
2-(2,5-dimethylpyrrol-1-yl)-5-oxiranylpyridine



To the ketone from example 39 (1.34g, 5.4mmol) dissolved in dry THF (20ml), cooled to 0°C, was added sodium borohydride (308mg, 8.1mmol) portionwise. The reaction mixture was stirred for 2 hours then 3M NaOH (aq) (10ml) was added and stirring continued for a further 16 hours. The reaction mixture was extracted with ethyl acetate (2 x 20ml) and the combined organic extracts washed with brine (5ml), dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with ethyl acetate: pentane (1:5) to give the title compound as a colourless oil (900mg, 4.2mmol, 78%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 2.13 (s, 6H), 2.91 (dd, 1H), 3.25 (t, 1H), 3.98 (t, 1H), 5.90 (s, 2H), 7.20 (d, 1H), 7.62 (dd, 1H), 8.58 (s, 1H). LRMS: m/z 215 ($M-H^+$).

EXAMPLE 41

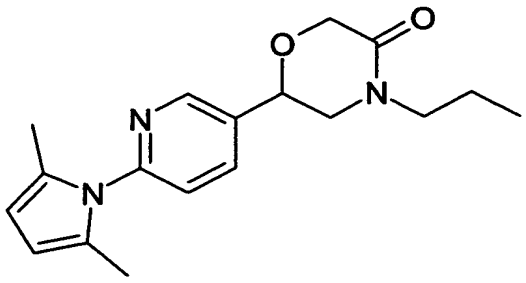
1-[6-(2,5-dimethylpyrrol-1-yl)pyridin-3-yl]-2-propylaminoethanol



To the epoxide from example 40 (900mg, 4.2mmol) in DMSO (5ml) was added propylamine (4ml, 4.8mmol) and the reaction mixture was heated to 40°C for 4 days. The reaction mixture was then cooled and 3M HCl (aq) (10ml) and water (10ml) were added before washing with diethyl ether (2 x 10ml). This organic layer was discarded. The aqueous layer was basified with NH_4OH (5ml) and extracted with ethyl acetate (3 x 10ml). The organic extracts were combined and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound as an oil (1.15g, 4.2mmol, 100%). ^1H NMR ($CDCl_3$, 400MHz) δ: 0.93 (t, 3H), 1.62 (m, 2H), 2.11 (s, 6H), 2.69-2.82 (m, 3H), 3.06 (dd, 1H), 3.60 (bs, 2H), 4.92 (dd, 1H), 5.84 (s, 2H), 7.20 (d, 1H), 7.88 (d, 1H), 8.61 (s, 1H). LRMS: m/z 274 ($M-H^+$).

EXAMPLE 42

6-[6-(2,5-dimethylpyrrol-1-yl)pyridin-3-yl]-4-propylmorpholi-3-one

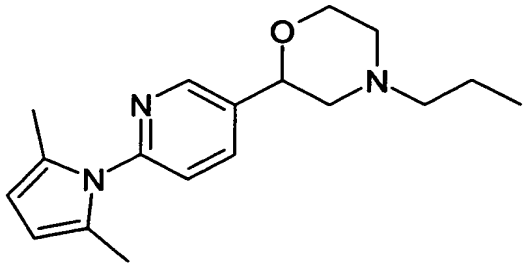


Prepared following the same method as for example 27 with the amine from example 41 (1.15g, 4.2mmol). Purification by column chromatography on silica eluting with dichloromethane: methanol (98:2) gave the title compound as a brown film (191mg, 0.61mmol, 14%). ^1H NMR ($CDCl_3$, 400MHz) δ: 0.97 (t, 3H), 1.65 (m, 2H), 2.13 (s, 6H), 3.38 (m, 1H), 3.42-3.56 (m, 2H), 6.61 (t, 1H), 4.35

(d, 1H), 4.45 (d, 1H), 4.91 (dd, 1H), 6.91 (s, 2H), 7.22 (d, 1H), 7.89 (d, 1H), 8.61 (s, 1H). LRMS: m/z 314 ($M-H^+$).

EXAMPLE 43

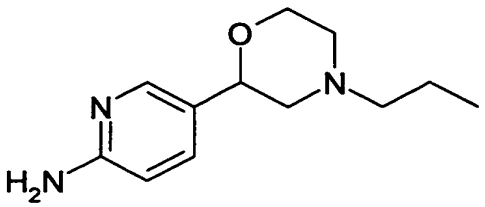
6-[6-(2,5-dimethylpyrrol-1-yl)pyridin-3-yl]-4-propylmorpholine



To a solution of the morpholin-3-one from example 42 (191mg, 0.61mmol) in dry THF (5ml) was added lithium aluminium hydride (1M solution in diethyl ether) (1.25ml, 0.61mmol) and the reaction mixture was warmed to reflux for 2.5 hours. The reaction mixture was cooled to room temperature then 1M NaOH (1.25ml) was added to give a white precipitate. The reaction mixture was filtered and concentrated *in vacuo.* The white solid was discarded. The concentrated filtrate was purified by column chromatography on silica eluting with dichloromethane: methanol (95:5) to give the title compound as a white film (108mg, 0.36mmol, 59%). ^1H NMR ($CDCl_3$, 400MHz) δ: 0.92 (t, 3H), 1.61 (q, 2H), 2.10 (s, 6H), 2.15 (m, 1H), 2.29 (dt, 1H), 2.40 (t, 2H), 2.82 (d, 1H), 3.02 (d, 1H), 3.90 (t, 1H), 4.08 (d, 1H), 4.71 (d, 1H), 5.89 (s, 2H), 7.20 (d, 1H), 7.81 (d, 1H), 8.60 (s, 1H). LRMS: m/z 300 ($M-H^+$).

EXAMPLE 44

5-(4-propylmorpholin-2-yl)pyridin-2-ylamine



To the 2,5-dimethylpyrrole from example 43 (45mg, 0.15mmol) in ethanol (3ml) was added hydroxylamine hydrochloride (52mg, 0.75mmol) and the reaction mixture heated to 80°C for 20 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with dichloromethane: methanol: ammonia (90:10:1) to give the title compound as a colourless film (31mg, 0.14mmol, 94%). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 0.92 (t, 3H), 1.60 (m, 2H), 2.11(t, 1H), 2.25 (dt, 1H), 2.41 (t, 2H), 2.82-2.91 (dd, 2H), 3.89 (dt, 1H), 4.01 (dd, 1H), 4.57 (bd, 3H), 6.49 (d, 1H), 7.42 (d, 1H), 8.02 (s, 1H). LRMS: m/z 222 ($M-H^+$).